#### Title: A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Selected Relapsed or Refractory Hematological Malignancies

AMG 397 Amgen Protocol Number AMG 397 20170173 IND 137128 Eudra CT 2017-005035-16

Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805-447-1000
Key Sponsor Contacts:	, MD Early Development Lead Phone: E-mail:
	Clinical Research Study Manager Phone: E-mail:
<b>Date:</b> Amendment 1	30 November 2017 <b>28 March 2018</b>

# **Confidentiality Notice**

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1-800-77-AMGEN, Canadian sites, 1-866-50-AMGEN; Amgen's general number in the US (1-805-447-1000).

NCT Number: NCT03465540 This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov



#### Investigator's Agreement

I have read the attached protocol entitled "A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects with Selected Relapsed or Refractory Hematological Malignancies", dated 28 March 2018, and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)



#### **Protocol Synopsis**

**Title:** A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Selected Relapsed or Refractory Hematological Malignancies

#### Study Phase: 1

**Indications:** Relapsed or Refractory (RR) Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL) or Acute Myeloid Leukemia (AML)

#### **Primary Objectives:**

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397

#### Secondary Objectives:

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

#### **Exploratory Objectives:**

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- Identify metabolite(s) of AMG 397 in plasma and urine
- Demonstrate AMG 397 inactivation of myeloid cell leukemia sequence 1 (MCL1) by the activation of BAX and caspase 3 in circulating monocytes or blast cells, and/or the decrease of circulating monocytes
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary

#### Hypothesis:

A safe and tolerable dose of AMG 397 will have evidence of anti-tumor activity in patients with selected RR hematological malignancies as measured by Objective Response Rate (ORR).

#### Primary Endpoints:

 Incidence of dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events and clinically-significant changes in vital signs, physical examinations, electrocardiogram (ECGs) and clinical laboratory tests

#### Secondary Endpoints:

- Efficacy parameters:
  - ORR using response criteria per the following:
    - International Myeloma Working Group (IMWG) for MM subjects
    - Lugano Classification for NHL subjects
    - Revised International Working Group (IWG) for AML subjects
  - Duration of response
  - Progression Free Survival (PFS) and Overall Survival (OS)
- AMG 397 PK parameters including, but not limited to, maximum observed concentration (C<sub>max</sub>), time of maximum observed concentration (T<sub>max</sub>), area under the concentration-time curve (AUC), clearance (CL) and half-life (t<sub>1/2</sub>)



#### **Exploratory Endpoints:**

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

#### Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle in adult subjects with selected RR hematological malignancies.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

The study will be conducted at up to 20 sites globally in Australia, Europe, Japan, and the United States (US). Other countries or regions may be added.

#### Dose Escalation-Part 1

Dose escalation will estimate MTDs for Groups 1A and Group 1B using an adaptive, BLRM design. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on dose escalation/change. The table below shows the planned dose levels for dose escalation.

Dose Cohort Levels	Dose (mg)
1	80
2	160
3	320
4	640

Planned Doses per Dose Cohort Level
-------------------------------------

Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg with enrollment from Group 1A and 1B. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 28 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.



Dose escalation for both Group 1A and 1B will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

There is a potential for tumor lysis syndrome (TLS) in subjects with hematologic malignancies, especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS:

- Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397.
- Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.
- For the management of TLS, please refer to Section 6.5.7 for more details

The DLRT will convene to review the safety data and may determine a lead-in dose, which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

**NOTE:** Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

#### Intra-subject Dose Escalation

Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the PI and sponsor, as long as no DLT has been reported for this subject during or after completion of the DLT period.

#### Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed in groups with selected RR hematological malignancies below:

- Group 2A will consist of subjects with MM
- Group 2B will consist of NHL subjects with Diffuse Large B-cell Lymphoma (DLBCL)
- Group 2C will consist of subjects with AML

Dose expansion in all of these groups may take place concurrently. The maximum tolerated dose (MTD) for each indication, identified from the dose escalation phase, will inform the dose expansion phase.

#### Sample Size:

Up to 90 evaluable subjects will be enrolled in the study. Up to 60 evaluable subjects will be enrolled during dose escalation (up to 30 in both Groups 1A and 1B). Up to 30 evaluable subjects will be enrolled into the dose expansion part (up to 10 each for Groups 2A, 2B, and 2C).



Male or female subjects  $\geq$  18 year of age at the time of informed consent who have RR MM, NHL and AML. For a full list of eligibility criteria, refer to Section 4.1 and Section 4.2.

#### Investigational Product

AMG 397 is a potent and selective inhibitor of protein-protein interactions between myeloid cell leukemia sequence 1 (MCL1) and pro-apoptotic members of the lymphoma/leukemia 2 (Bcl-2) family. AMG 397 is an oral agent which will be provided as 5 mg, 20 mg, and 100 mg tablets, and will be packaged in bottles of 15 tablets.

#### Amgen Investigational Product Dosage and Administration:

AMG 397 is administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle at dose levels detailed in Table 3.

#### **Procedures:**

For all subjects, after written informed consent has been obtained, all screening tests and procedures will be performed within 21 days of administration of the first dose of AMG 397 (day 1), unless otherwise noted. Once a subject is enrolled into the study, serial clinical safety and study evaluations as per the Schedule of Assessments (Table 4 and Table 5) will be performed including physical examination, vital signs, clinical laboratory tests, ECGs, and sample collections. This treatment period will continue until the subject becomes intolerant to the investigational product, signs and symptoms of clinical progression are evident as determined by the investigator, or the subject withdraws consent. An end of treatment (EOT) visit will be conducted immediately after the decision to discontinue treatment with AMG 397.

If applicable, the subject will return 28 (+7) days after the last dose of AMG 397 for the Safety Follow-Up (SFU) visit.

In dose expansion part only, long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent to assess for survival and/or the commencement of subsequent cancer therapy.

For a full list of study procedures, including the timing of each procedure, please refer to the Schedule of Assessments (Table 4 and Table 5) Section 7.1.

#### Statistical Considerations:

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study. During dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic,

efficacy and biomarker data by dose, dose schedule, and time as appropriate. Descriptive

statistics on continuous data will include means, medians, standard deviations and ranges, while

categorical data will be summarized using frequency counts and percentages. ORR will be

presented with 80% exact CI. PFS and OS will be summarized using the Kaplan-Meier method. Descriptive statistics will be provided for duration of response (DOR) and DOR summarized by the Kaplan-Meier method, as appropriate.

Graphical summaries of the data may also be presented.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc.

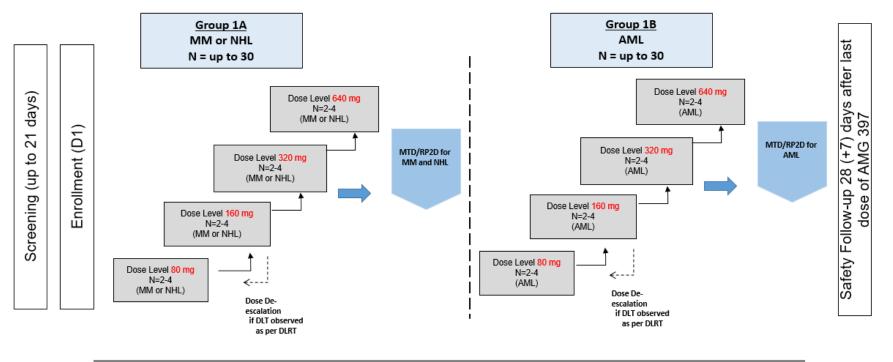


#### Study Design and Treatment Schema

### Figure 1. Study Design and Treatment Schema

# **Dose Escalation – Part 1\*:**

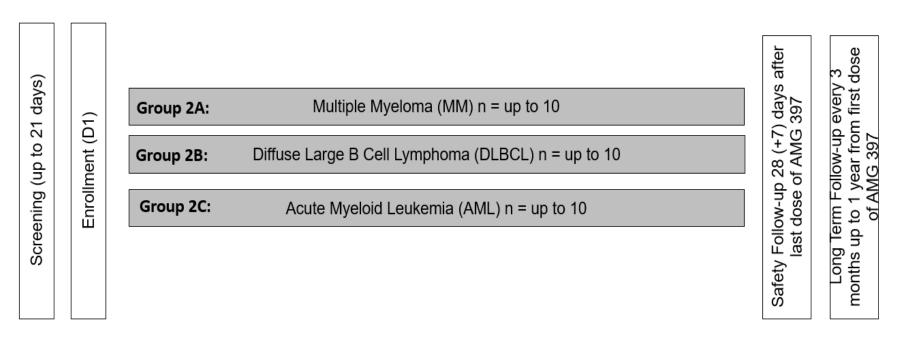
An Amgen representative will notify the sites in writing when a cohort is open to screen new subjects.



Treatment with AMG 397

4-week cycles of AMG 397 until progression of disease, unacceptable toxicity, withdrawal or death \*No lead-in dosing is implemented

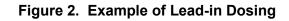
# **Dose Expansion – Part 2:**

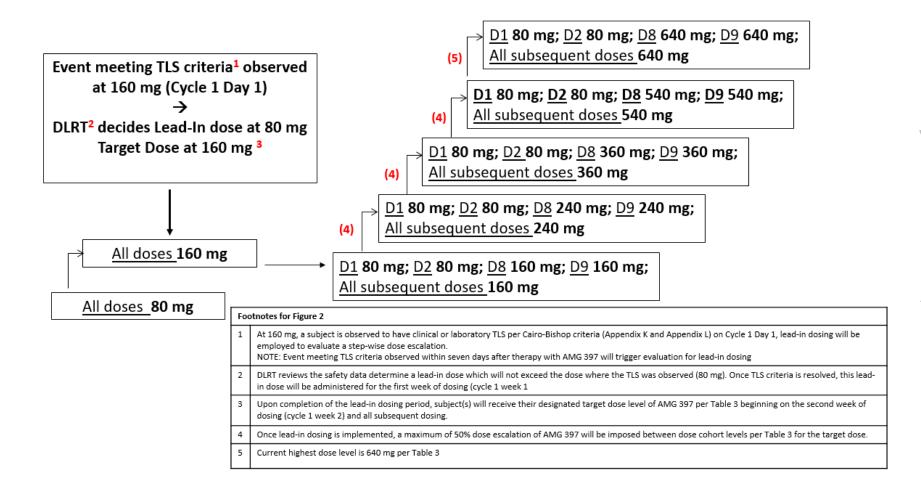


Treatment period with AMG 397 using the MTDs for MM, DLBCL, and AML from Part 1

4-week cycles of AMG 397 until progression of disease, unacceptable toxicity, withdrawal or death









# Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
APML	Promyelocytic leukemia
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
BP	blood pressure
CBC	complete blood count
CECT	Contrast-enhanced computed tomography
CI	confidence interval
CL	Clearance
C <sub>max</sub>	maximum observed concentration
Cmin	minimum observed concentration
CR	complete response
Cri	Complete response/remission with incomplete recovery of peripheral blood counts
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DILI	drug-induced liver injury
DLBCL	Diffuse Large B-cell Lymphoma
DLRM	dose level review meeting
DLRT	dose level review team
DLT	dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ЕСНО	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European Leukemia Net
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject.



Abbreviation or Term	Definition/Explanation
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
End of Study (primary completion)	defined as when the last subject is assessed or receives an Intervention for the purposes of final collection of data for the primary endpoints.
End of Study	defined as when the last subject completes the safety follow-up assessments
EOI	End of infusion
eSAE	electronic serious adverse event
ESR	erythrocyte sedimentation rate
FIH	first in human
FISH	fluorescent in situ hybridization
FLC	serum light chain
FU	follow-up
GCP	Good Clinical Practice
h, hr	Hour
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
heart rate / HR	number of cardiac cycles per unit of time
HepCAb	hepatitis C antibody
HIDAC	high dose cytarabine
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ІСН	International Conference on Harmonisation
IEC	Independent Ethics Committee
lg	Immunoglobulin
IMWG	International myeloma working group
IMWG-URC	International myeloma working group uniform response criteria
IND	Investigational new drug
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous or roman numeral 4
LAIP	Leukemia-associated immunophenotype
LTFU	Long-term follow-up
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MCL1	Myeloid Leukemia Cell 1



Page	12	of	130
------	----	----	-----

Abbreviation or Term	Definition/Explanation
Mg	Milligrams
ММ	Multiple myeloma
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N, n	Number
NHL	Non-Hodgkin's Lymphoma
ORR	Overall response rate
PD	phramacodynamic
РК	pharmacokinetics
PR	partial response
PR	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG or partial response
РТ	prothrombin time
QRS	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc	QT interval corrected for heart rate using accepted methodology
QTcF	QT interval corrected for heart rate using Fridericia's formula
QW	Once weekly
RBC	red blood cells
RP1BD	recommended phase 1b dose
RP2D	recommended phase 2 dose
RR	Relapsed or refractory
SAE	Serious adverse event
sCR	stringent complete response
SD	standard deviation
SFLC	serum free light chain
SFU	Safety follow-up
SOA	Schedule of assessments
SPEP	serum protein electrophoresis
T <sub>1/2</sub>	half-life
TBL	total bilirubin
ТВА	Total Bile Acid
TLS	Tumor lysis syndrome



Abbreviation or Term	Definition/Explanation
t <sub>max</sub>	time of maximum observed serum concentration
UA	urinalysis
ULN	upper limit of normal
UPEP	urine protein electrophoresis
WBC	White blood cell
WHO	World Health Organization



# TABLE OF CONTENTS

Proto	ocol Syr	nopsis		3		
Stud	y Desig	n and Trea	atment Schema	7		
Stud	y Gloss	ary		10		
1.	OBJE0 1.1 1.2 1.3	JECTIVES				
2.	BACK 2.1		AND RATIONALE Multiple Myeloma Background Non-hodgkin's Lymphoma Background Acute Myeloid Leukemia Background	20 20 22		
	2.2	AMG 397 2.2.1 2.2.2 2.2.3 2.2.4	Product Background AMG 397 Preclinical Pharmacology Pharmacokinetics AMG 397 Preclinical Toxicology	24 25 26 27		
	2.3		Dose Selection Rationale 2.3.1.1 Starting and Maximum Planned Doses	30 31		
	2.4	Clinical H	lypothesis	33		
3.	EXPER 3.1 3.2 3.3 3.4 3.5	Study De Number o Number o Replacen	L PLAN. sign	33 35 35 35 36 36		
4.	SUBJE 4.1 4.2	IECT ELIGIBILITY				
5.	SUBJE 5.1	UBJECT ENROLLMENT				
6.	TREAT	EATMENT PROCEDURES				



6.2	Investig	gational Proc	duct	42
	6.2.1	·	nvestigational Product AMG 397	
		6.2.1.1	Dosage, Administration, and Schedule	
		6.2.1.2	Dose-cohort Study Escalation and	
			Stopping Rules	45
		6.2.1.3	Dosage Adjustments, Delays, Rules for	
			Withholding or Restarting, Permanent Discontinuation	46
		6.2.1.4	Dose Stopping Rules	
6.3	Other F		juired Therapies	
0.0	6.3.1		ng requirements for AMG 397	
6.4			cities	
6.5		-	agement Guidelines for AMG 397	
	6.5.1		estinal Toxicity	
	6.5.2		rrow Toxicity	
	6.5.3		ctive Toxicity- Male	
	6.5.4		g interactions	
	6.5.5	-	liary Toxicity	
	6.5.6		scular Toxicity	
	6.5.7		/sis Syndrome (TLS)	
6.6	Suppor		elines for AMG 397	
	6.6.1	Manager	nent of Infections	55
	6.6.2	Manager	nent of Renal Toxicities	56
6.7	Hepato	toxicity Stop	pping and Rechallenge Rules	56
	6.7.1		or Permanent Withholding of AMG 397 due to Hepatotoxicity	56
	6.7.2		or Conditional Withholding of AMG 397 due to	
			Hepatotoxicity	57
	6.7.3		or Rechallenge of AMG 397 After Potential	
		•	oxicity	58
6.8			ру	
6.9			5	
6.10	Exclude	ed Treatmer	nts and Procedures During Study Period	59
STUE	OY PROC	EDURES		59
7.1	Schedu	le of Asses	sments	59
7.2	Study F	Procedures.		70
	7.2.1	Medical I	History	70
	7.2.2	Prior The	erapy	70
	7.2.3	Physical	Examinations	70
	7.2.4	Height M	easurements	70
	7.2.5	-	leasurements	
	7.2.6	-	าร	
	7.2.7	Electroca	ardiogram Performed in Triplicate	71

7.



		7.2.8		ogram (ECHO) / Multigated Acquisition	72	
		7.2.9	Dosing Di	ary Review	72	
		7.2.10	Assessme	ents in MM Subjects	72	
			7.2.10.1	Serum Protein Electrophoresis (SPEP) and Urine Protein Electrophoresis (UPEP)	72	
			7.2.10.2	Serum Free Light Chain		
			7.2.10.3	Quantitative Immunoglobulin	72	
			7.2.10.4	Beta-2 Microglobulin.	73	
			7.2.10.5	Skeletal Survey	73	
			7.2.10.6	Bone marrow.	73	
		7.2.11	Assessme	ents in NHL Subjects	73	
			7.2.11.1	Imaging and Disease assessments	73	
			7.2.11.2	MRI Brain	74	
			7.2.11.3	Lymph Node and Bone Marrow Assessments	74	
			7.2.11.4	Whole Blood Plasma	74	
		7.2.12	Assessme	ents in AML Subjects	75	
			7.2.12.1	Disease Response in AML Subjects	75	
		7.2.13	Pharmaco	kinetic Blood Sampling	75	
		7.2.14	Blood Sar	nples	75	
		7.2.15	Clinical La	boratory Assessments	77	
	7.3	Biomar	ker Developr	nent	78	
		7.3.1	Blood Sar	nples	78	
		7.3.2	Bone Mar	row	79	
		7.3.3	Tumor Bio	psy	79	
	7.4	Genera	I Study Proc	edures	80	
		7.4.1	Screening		80	
		7.4.2	Treatment	t	80	
		7.4.3	End of Tre	eatment Visit	81	
		7.4.4	Safety Fol	low-Up (SFU) Visit	82	
		7.4.5	Long-term	Follow-up (Dose expansion subjects only)	82	
	7.5	Pharma	acogenetic Si	udies	82	
	7.6	Sample	e Storage and	Destruction	82	
8.	WITH	HDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY				
	8.1	Subjects' Decision to Withdraw			84	
	8.2	Investigator or Sponsor Decision to Withdraw or Terminate				
		Subject	84			
	8.3	Reasor	ns for Remov	al From Treatment or Study	85	
		8.3.1	Reasons f	or Removal From Treatment	85	
		8.3.2	Reasons f	or Removal From Study	85	
9.	SAFE			ON, RECORDING, AND REPORTING	85	



	9.1	9.1       Definition of Safety Events         9.1.1       Adverse Events					
		9.1.2	Serious A	dverse Events	86		
	9.2	Safety E	vent Repor	ting Procedures	87		
		9.2.1	Adverse E	Events	87		
			9.2.1.1	Reporting Procedures for Adverse Events That do not Meet Serious Criteria	87		
			9.2.1.2	Reporting Procedures for Serious Adverse Events	88		
			9.2.1.3	Reporting Serious Adverse Events After the Protocol-required Reporting Period	89		
	9.3	Pregnan	cy and Lac	tation Reporting	89		
10.	STATI			ATIONS	00		
10.	10.1						
	10.1	10.1.1	-	Sets			
	10.2		-	groups			
	10.2			- ·			
	10.0	Sample Size Considerations Adaptive Design					
	10.5	Planned Analyses					
	10.0	10.5.1	-	nalyses			
		10.5.2		el Review Team (DLRT)			
		10.5.3		nalysis			
		10.5.4		lysis			
	10.6			f Analysis			
		10.6.1		Considerations			
		10.6.2	Primary E	ndpoints	94		
		10.6.3		y Endpoints			
			10.6.3.1	Efficacy Endpoint Analyses	95		
			10.6.3.2	Pharmacokinetics Data Analysis	96		
		10.6.4	Explorato	ry Endpoints	96		
11.	PECU			ONS	06		
	11.1			5113			
	11.2			Board/Independent Ethics Committee			
	11.3			lity			
	11.4	-		bry Obligations			
12.				EGAL OBLIGATIONS			
	12.1			nts and Study Termination			
	12.2	•		on and Archive			
	12.3			nd Data Collection			
	12.4	_		sibilities for Data Collection			
	12.5	2.5 Language					



		Publication Policy	
13.		RENCES	
14.	APPE	NDICES	

# List of Tables

Table 1.	Binding Activity and Selectivity Profile of AMG 397 in a BIM Binding Assay	26
Table 2.	Predicted Human Exposures and Exposure Multiples at Steady-state After Oral Dosing of AMG 397	32
Table 3.	Planned Doses per Dose Cohort Level	33
Table 4.	Schedule of Assessments	60
Table 5.	Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)	64
Table 6.	Approximate Blood Volumes Collected for MM Subjects Only	76
Table 7.	Approximate Blood Volumes Collected for NHL Subjects Only	76
Table 8.	Approximate Blood Volumes Collected for AML Subjects Only	77
Table 9.	Clinical Laboratory Assessments	77
Table 10	<ol> <li>Stopping Boundary for Dose Expansion With Posterior Probability of 90% and Grade 4 or Higher Adverse Event Limit of 20%</li> </ol>	93
Table 11	. Operating Characteristics With Batch Size of 10 Subjects	93

# List of Figures

Figure 1.	Study Design and Treatment Schema	7
Figure 2.	Example of Lead-in Dosing	9

# List of Appendices

Appendix A.	Additional Safety Assessment Information	109
Appendix B.	eSerious Event Contingency Form	111
Appendix C.	Pregnancy and Lactation Notification Worksheets	114
Appendix D.	Operating Characteristics for 2-Parameter BLRM Design	116
Appendix E.	International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC)	119
Appendix F.	ECOG Performance Status and NYHA Classification	121
Appendix G.	Definition of Relapsed or Refractory Progressive Disease and Line of Therapies	122
Appendix H.	World Health Organization Classification for Acute Myeloid Leukemia	124
Appendix I.	Response Assessment per the Lugano Classification for NHL	126



Appendix J.	European Leukemia Network (ELN) Response Criteria in AML (2017)	
Appendix K.	Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading	
Appendix L.	Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome	130



## 1.1 Primary

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397

# 1.2 Secondary

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

## 1.3 Exploratory

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- Identify metabolite(s) of AMG 397 in plasma and urine
- Demonstrate AMG 397 inactivation of MCL1 by the activation of BAX and caspase 3 in circulating monocytes or blast cells, and/or the decrease of circulating monocytes
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary

# 2. BACKGROUND AND RATIONALE

#### 2.1 Disease

# 2.1.1 Multiple Myeloma Background

Multiple myeloma is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, production of a monoclonal protein present in the blood or urine and associated organ dysfunction (Palumbo and Anderson 2011).

Multiple myeloma is the second most common (10-15%) hematological cancer. It is responsible for 15-20% of all deaths from hematological cancer and about 2% of all cancer deaths. Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Survival is improving, with median overall survival in the range of 7-10 years after initial diagnosis. Nevertheless, myeloma remains an incurable cancer, and with subsequent relapses, the disease becomes refractory to current treatments. Therefore, RR multiple myeloma is still an unmet medical need (Smith and Yong 2013).



Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011). Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires clinical observation. Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma. Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for subjects under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction. Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older subjects or those with coexisting conditions. Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in subjects over 75 years of age or in younger subjects with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011).

Treatment of RR MM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical. Several new agents and targets are currently under development and show considerable promise. In the past 5 years, carfilzomib, pomalidomide, elotuzumab, ixazomib, daratumumab, were granted approval by US FDA for RR MM. , Despite advances in the management of multiple myeloma, however, relapse is inevitable in almost all subjects.



Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos, 2015). Thus, there remains an urgent need for treatment options for patients with RR MM.

# 2.1.2 Non-hodgkin's Lymphoma Background

About 74,680 people (41,730 males and 32,950 females) will be diagnosed with Non Hodgkin's Lymphoma (NHL), and about 19,910 people will die from this malignancy. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for 30% to 40% of cases and 13% of all hematologic disorders. The incidence is approximately 8 cases per 100,000 and rises with age; the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Morphologically similar entities have historically been treated in a similar manner as DLBCL, and thus are collectively known as aggressive B-cell lymphomas. DLBCL, as a uniform diagnostic entity, makes up approximately 85% of aggressive B-cell lymphomas (Ziepert et al, 2010). However, distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications (Swerdlow et al, 2016). Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975). Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015). Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive either high dose chemotherapy (HDT) with autologous HSCT or allogeneic HSCT (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been as used as 1 criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). It is not known if responsiveness to newer classes of therapies, such as those that are immune-based, may also be sufficient to permit the successful use of HDT.

The most commonly used regimens in the S1 treatment of transplant-eligible patients contain rituximab and a platinum-based agent such as cisplatin (eg, R-DHAP, R-GDP, R-ESHAP) or carboplatin (eg, R-ICE) (Crump et al, 2014; Martin et al, 2008;



Witzig et al, 2008; Kewalramani et al, 2004). Patients who do not respond to S1 may be offered alternative therapies (hereafter referred to as S2) and HSCT provided that there is a response to S2 and that performance status and organ function are relatively preserved. There is no standard S2 regimen for transplant eligible patients. The ESMO and NCCN guidelines are relatively silent on appropriate S2 regimens (Zelenetz et al, 2016; Tilly et al, 2015). Results of small, single-center retrospective analyses support the conclusion that standard cytotoxic therapy is of limited value in patients not responsive to S1 chemotherapy and that novel therapies should be explored in this setting (Elstrom et al, 2010; Ardeshna et al, 2005;).

## 2.1.3 Acute Myeloid Leukemia Background

Acute myeloid leukemia (AML) is characterized by accumulation of abnormal blasts in the marrow. These cells disrupt normal hematopoiesis, thus contributing to the bone marrow failure that is the most common underlying cause of death. The abnormal blasts can escape into the peripheral blood, and may infiltrate organs. Diagnosis is based on demonstration that the marrow or blood has >20% blasts of myeloid origin (Estey, 2016) AML is the most common form of acute leukemia in adults in the United States (US).

In 2017, an estimated 21,380 new cases of AML are expected in the US with approximately 10,590 deaths from this disease (American Cancer Society, 2017). Outcomes for most subjects with AML remain poor (Burnett et al, 2011a). In particular, relapsed disease is associated with unsatisfactory outcomes in the majority of subjects (Ravandi, 2013). Although the majority of subjects with AML initially achieve CR, over 60% will eventually relapse after a variable period of remission. Using the traditional cytotoxic chemotherapy regimens, the likelihood of achieving a second CR is low especially if the first CR was short in duration, particularly if less than one year (Estey et al, 1996).

This is particularly true for subjects who have primary refractory disease and have never achieved a morphological response. For example, subjects with AML refractory to one course of high dose cytarabine (HiDAC) containing regimen have a median overall survival of only 3.8 months (Ravandi et al, 2010). Subjects whose initial CR duration is more than one year have been traditionally treated with HiDAC containing salvage regimens but only a minority achieve a second CR and many are not candidates for a potentially curative allogeneic hematopoietic stem cell transplant (HSCT) performed in second CR (Estey, 2000). Apart from duration of first CR, other predictors of outcome in first relapse include age, cytogenetics, and whether the patient received an allogeneic



HSCT in first CR (Breems et al, 2005). However, in the study reported by (Breems et al, 2005), only a minority of subjects with AML in first relapse had a successful long-term outcome and the long-term prognosis of the majority of subjects with relapsed or refractory AML remains dismal.

## 2.2 AMG 397 Product Background

AMG 397 is a potent and selective inhibitor of protein-protein interactions between MCL1 (myeloid cell leukemia sequence 1) and pro-apoptotic members of the B-cell lymphoma/leukemia 2 (Bcl-2) family. Programmed cell death or apoptosis is regulated via a complex network of protein-protein interactions between the pro-and anti-apoptotic sub-groups that make-up the Bcl-2 protein family. (Kozopas, Yang et al. 1993, Strasser, Cory et al. 2011, Czabotar, Lessene et al. 2014). MCL1 is an anti-apoptotic member of this family and promotes cell survival. In contrast, pro-apoptotic family members, such as Bak, Bax, or the Bcl-2 homology 3 (BH3)-only protein family members, such as BIM and PUMA, are critical effectors for the induction of apoptosis. Upon the induction of apoptotic stimuli, pro-apoptotic BH-3 only proteins bind MCL1 and other pro-survival Bcl-2 family members, disrupting interactions between MCL1 and the pro-apoptotic effector proteins, Bak and Bax. This leads to activation and oligomerization of Bak and Bax, mitochondrial outer membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Strasser, Cory et al. 2011) (Czabotar, Lessene et al. 2014).

Malignant transformation results in cellular stress from a variety of pro-apoptotic insults, including hypoxia and gain-of-function mutations in oncogenes, suggesting there is a strong selective advantage for tumors to evolve mechanisms that culminate in the evasion of apoptosis. The over-expression of anti-apoptotic Bcl-2 family members, such as MCL1 and Bcl-2, has emerged as a central mechanism by which cancers buffer pro-apoptotic stress. There is now considerable data suggesting that MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers. Genetic ablation of MCL1 has been shown to protect mice from the development of acute-myeloid leukemia (AML) (Glaser, Lee et al. 2012). Additional mouse knockout studies have implicated MCL1 in the maintenance of plasma cells, an observation that suggests MCL1 may be a critical pro-survival factor in multiple myeloma (Peperzak, Vikstrom et al. 2013). MCL1 is highly expressed in a variety of human tumors, and over-expression of MCL1 has been implicated in resistance to chemotherapy and to Bcl-2/Bcl-xL inhibitors (van Delft, Wei et al. 2006,



Wertz, Kusam et al. 2011). Finally, focal amplification of the MCL1 gene has been observed in up to 10% of cancers derived from multiple tissue types, including lung and breast (Beroukhim, Mermel et al. 2010). These data suggest that the inhibition of MCL1 represents a novel and compelling therapeutic strategy for the treatment of cancer. A promising strategy for targeting MCL1 takes advantage of specific small molecules that selectively bind to MCL1 and disrupt its interactions with the BH3 domain of pro-apoptotic partner proteins such as Bak, and Bim, leading to the activation of the intrinsic apoptotic cascade and death in cells dependent on MCL1 for survival. The MCL1 inhibitor AMG 397 is a first in class therapeutic with novel MOA (disruption of protein-protein interactions) with the potential to directly induce apoptosis in cells dependent on MCL1 for survival, Furthermore, the activity of AMG 397 in pre-clinical models suggests that AMG 397 may have utility in hematological malignancies, particularly multiple myeloma, NHL and AML.

Refer to the specific section of the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(S)

# 2.2.1 AMG 397 Preclinical

AMG 397 neutralizes the interaction between human MCL1 and Bim in a biochemical TR-FRET based assay with an IC50 of 0.116 nM in serum free conditions. In addition, AMG 397 exhibits comparable potency against cynomolgus monkey, dog and rabbit Mcl 1, but is less potent against mouse and rat MCL1 in a serum free TR-FRET-based potency assay (IC50 values of 0.380, 0.112, and 0.144, 22.4 and 221 nM for dog, monkey, rabbit, rat and mouse MCL1, respectively) (Table 1) (Study R20150152). Examination of the AMG 397 binding pocket in human MCL1 suggests a leucine residue at amino acid position 248 contributes to the high affinity interaction between AMG 397 and human MCL1. In mouse and rat MCL1, the corresponding amino acid is a phenylalanine, which may contribute to the reduced affinity of AMG 397 for rat and mouse MCL1 (Study R20150152). AMG 397 is highly selective for MCL1 over the related Bcl-2 family members, Bcl-2 and Bcl-xL, exhibiting IC50 values of > 5000 nM in a TR-FRET BIM binding assay (Study R20150153) (Table 1).

Binding Activity and Selectivity Profile in Cell-Free TR-FRET Bim Binding Assays	AMG 397	
Human MCL1 IC <sub>50</sub> (nM)	0.116	
Dog MCL1 IC₅₀ (nM)	0.380	
Monkey MCL1 IC50 (nM)	0.112	
Rabbit MCL1 IC₅₀ (nM)	0.144	
Mouse MCL1 IC <sub>50</sub> (nM)	221	
Rat MCL1 IC₅₀ (nM)	22.4	
Human Bcl-2 IC₅₀ (nM)	> 5000	
Human Bcl-xL IC <sub>50</sub> (nM)	> 5000	

# Table 1. Binding Activity and Selectivity Profile of AMG 397 in a BIM Binding Assay

Bcl-2 = B-cell lymphoma-2; Bcl-xL = B-cell lymphoma- extra-large;  $IC_{50}$  = half maximal inhibitory concentration; MCL1= Myeloid Cell Leukemia 1; TR-FRET = time-resolved fluorescence energy transfer The  $IC_{50}$  values of AMG 397 were determined from duplicate measurements by fitting concentration-response data of individual replicates with a four-parameter sigmoidal model in Genedata Screener (Genedata, Basel, Switzerland). *Source: Study R20150152 and Study R20150153* 

AMG 397 inhibited the interaction between MCL1 and Bak in transfected HEK 293M cells with a mean IC50 of 71.1 nM in serum free growth medium (Study R20150154). Upon AMG 397 treatment for 16 hours, OPM-2 cell viability was reduced in a dose dependent manner under all conditions tested (ie, serum-free, with 10% FBS (1) and with 5% HS). The IC50 values of AMG 397 induced cell death were determined to be  $0.020 \pm 0.039 \mu$ M in the absence of serum,  $0.0946 \pm 0.025 \mu$ M in the presence of 10% FBS and  $0.159 \pm 0.039 \mu$ M in the presence of 5% HS (Study R20150154).

# 2.2.2 Pharmacology

AMG 397 interacted in vitro with several off-target receptors; however, none of these is expected to result in clinically significant effects over the proposed clinical dose range. The AMG 397 hERG 50% inhibition concentration ( $IC_{50}$ ) was > 1.1  $\mu$ M, the highest tested concentration that could be evaluated, thus, no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range. In an isolated rabbit heart study, the no-effect concentration was 1  $\mu$ M; thus, no clinically significant effects on cardiac electrical or functional activity over the proposed clinical dose range are expected. There were no AMG 397-related changes in electrocardiograms (ECGs), respiratory rate, or neurological clinical signs in the GLP 23-day dog toxicology study conducted at doses up to 15 mg/kg.



### 2.2.3 Pharmacokinetics

AMG 397 was characterized in vitro and in vivo preclinical studies. In animal species AMG 397 had low clearance (CL) relative to hepatic blood flow, moderate volume of distribution (Vss) and mean terminal elimination half-life ( $t_{1/2z}$ ) ranging from 8.3 to 19 hour. The observed bioavailability was variable across species ranging from 23% in dogs and monkeys, 39% in rats and 56% in mice. In vitro, AMG 397 was highly bound to plasma proteins in all species including human (mean fraction unbound ranging from 0.0048 to 0.027), and did not partition into red blood cells. These data were used to predict the human AMG 397 PK parameters, with a CL of 0.057 L/hr/kg, Vss of 1.0 L/kg, and  $t_{1/2z}$  of 12 hours. Bioavailability after oral dosing was estimated to be 31%, an average across preclinical species.

AMG 397 was an inducer of CYP2B6, CYP2C9, and CYP3A4, and reversible inhibitor of CYP2B6, CYP2C8, and CYP3A4 in vitro while it was not an inhibitor of other major drug metabolizing human CYP enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. AMG 397 was also a time-dependent inhibitor of CYP3A4 but not of any of the other CYPs tested. Additionally, AMG 397 was identified as an inhibitor of P-gp ( $IC_{50}$  of 8.7 µM). For BCRP, MATE1, MATE2-K, and OATP1B1, incomplete inhibition (36 - 54%) was observed at the highest test concentration (100 µM) of AMG 397, suggesting weak inhibition. Considering dose levels and frequency, based on physiologically based pharmacokinetic modelling, it was determined that AMG 397 has a potential to interact with CYP3A4 and P-gp.

# 2.2.4 AMG 397 Preclinical Toxicology

AMG 397 was well tolerated in a GLP 23-day rat toxicology study conducted at doses of 5, 15 and 500 mg/kg. The severely toxic dose in 10% of the animals (STD10) was ≥ 500 mg/kg. Key AMG 397-related findings in the rat included minimally to moderately increased serum transaminases and bilirubin that were associated with periportal vacuolation of hepatocytes, dilatation of lacteals and hypertrophy/hyperplasia of the mucosa in the small intestine, dilatation of the subcapsular space of the mesenteric lymph node, and atrophy of the zona glomerulosa of the adrenal gland. AMG 397-related changes in the rat fully or partially reversed by the end of a 28-day recovery period.

In an exploratory 14-day dog toxicology study, 30 mg/kg was poorly tolerated (liquid stools, decreased food consumption, body weight loss) that resulted in early euthanasia and/or early termination of dosing of some animals. AMG 397 was generally well



tolerated in a GLP 23-day dog toxicology study at doses of 3, 7.5 and 15 mg/kg. The highest nonseverely toxic dose (HNSTD) in dogs was 15 mg/kg. Key AMG 397-related findings in the dog included soft feces, dose-dependent reductions in monocytes and other leukocyte subsets, minimally to mildly increased serum transaminase without light microscopic correlates in the liver, decreased lymphoid cellularity in lymphoid tissues, decreased bone marrow cellularity, vacuolation of the lamina propria of the small intestine, and dose-dependent decreased testes weight with the light microscopic correlate of tubular degeneration/atrophy of seminiferous tubules. Although the 23-day dog study did not include a recovery period, AMG 397-related changes are expected to be reversible based on the nature, incidence and severity of the changes.

AMG 397 was not mutagenic or clastogenic in exploratory genetic toxicology studies. AMG 397 was not photototoxic in rats.

Overall, the results of the nonclinical safety studies support the initiation of AMG 397 clinical trials and the initial clinical plan.

## Risk Assessment

AMG 397 interacted in vitro with several off-target receptors; however, none of these is expected to result in clinically significant effects over the proposed clinical dose range. The AMG 397 hERG 50% inhibition concentration ( $IC_{50}$ ) was > 1.1 µM, the highest tested concentration that could be evaluated, thus, no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range. In an isolated rabbit heart study, the no-effect concentration was 1 µM; thus, no clinically significant effects on cardiac electrical or functional activity over the proposed clinical dose range are expected. There were no AMG 397-related changes in electrocardiograms (ECGs), respiratory rate, or neurological clinical signs in the GLP 23-day dog toxicology study conducted at doses up to 15 mg/kg.

Potential risks are safety concerns based on mechanism of action, nonclinical data, or clinical data from AMG 397 or similar compounds that have either not yet been observed in human subjects or for which a causal association with AMG 397 has not yet been established. The potential risks and proposed clinical monitoring strategies are described below. All potential risks presented below have shown reversibility in preclinical studies:



#### **Gastrointestinal toxicity**

In the 23-day rat study, AMG 397 caused minimal to mild lacteal dilation in the small intestine. The lacteal dilation change may affect dietary lipid absorption and chylomicron synthesis (Boyle et al, 2012). In the 23-day dog study, AMG 397 caused mild vacuolation in the lamina propria of the small intestine. In an exploratory 14-day dog study, AMG 397 at a higher dose than used in the 23-day study was poorly tolerated due to GI clinical signs. There was no GI mucosal degeneration except in the pylorus where it was noted to be minimal to mild in the dog. Based on these observations, GI toxicity is a potential risk for patients.

#### Bone marrow toxicity

In early exploratory toxicology studies, a dose-dependent decrease in monocytes was seen in dogs. In the 23-day dog toxicology study, AMG 397-related decreased bone marrow cellularity with decreased lymphocytes, monocytes, and basophils was likely related to the primary pharmacology of AMG 397, ie, inhibition of MCL-1. White blood cell counts should therefore be monitored during clinical studies.

#### **Reproductive toxicity (Male)**

AMG 397 caused degeneration/atrophy of the seminiferous tubules with depletion of spermatogonia, spermatocytes, and spermatids of the testis along with decreased testicular weight in the dog. Patients should be advised of the potential effect on male fertility.

#### **Drug-drug interactions**

Data from in vitro nonclinical studies indicate that AMG 397 is an inhibitor of various CYP450s when tested in human liver microsomes. It is a reversible inhibitor of CYP2B6, CYP2C8, and CYP3A. AMG 397 is also a mechanism-based inhibitor of CYP3A4. Additionally, AMG 397 has the potential to be an inducer of CYP3A4, CYP2B6, and CYP2C9. It is also an inhibitor of the drug transporters, namely P-gp, MATE-1, and BCRP. AMG 397 is a substrate of P-gp and is expected to be predominantly eliminated as unchanged parent drug via biliary elimination.

Although AMG 397 inhibits multiple CYPs and transporters in vitro, based on physiologically based pharmacokinetic modeling and in considering predicted human PK and efficacious dose, AMG 397 has the potential to inhibit CYP3A and P-gp. Inhibition of other CYPs and transporters is unlikely to result in a drug-drug interaction.



## Hepatobiliary toxicity

AMG 397-related elevations in total bilirubin occurred in the rat. These changes were at times accompanied by increases in urinary bilirubin and increases in AST and ALT; however, there was only minimal periportal vacuolation in the liver. Serum transaminases were also increased in the dog but without accompanying bilirubin increases or correlative light microscopic changes in the liver.

# Cardiovascular toxicity

MCL1 is highly expressed in the myocardium, but its effect upon cardiac cells has not been established. In studies conducted in knockout mice with ablation of MCL-1, these animals showed reduced cardiac function. In mouse models, it has been suggested cardiac specific ablation of MCL1 resulted in fatal dilated cardiomyopathy manifested by a loss in cardiac contractility, abnormal mitochondria structure and abnormal mitochondrial respiration (Thomas et al, 2013; Wang et al, 2013). In the 23-day toxicology studies in the rat with AMG 397, reduction in cardiac weight was noted; however, there were no light microscopic correlates and no apparent clinical manifestations were noted. Additionally, no ECG, heart weight, or cardiac light microscopic changes were observed in dogs.

# **Tumor Lysis Syndrome**

Clinical tumor lysis syndrome has been observed in a clinical trial with a drug of the same mechanism of action. Subjects with a high tumor burden or compromised renal function (eg, International Staging System [ISS] Stage II/III) may be at elevated risk for tumor lysis syndrome.

Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed in all subjects and any pre-existing abnormalities must be corrected prior to starting treatment with AMG 397. In addition, subjects must be appropriately hydrated prior to each dose of AMG 397. Further details regarding mandatory tumor lysis syndrome prophylaxis are provided in the study protocol in Section 6.5.7.

# 2.3 Rationale

MCL1 is a member of the BCL2 family of proteins integral to the control of apoptosis (programmed cell death). MCL1 is an anti-apoptotic member of the BCL2 family and promotes cell survival. In contrast, pro-apoptotic family members, such as BAK and BAX are critical effectors for the induction of apoptosis. Upon apoptotic stimuli, pro-apoptotic BH-3 only proteins (eg, Bid) bind MCL1, and disrupt the interaction between MCL1 and BAK or BAX. This leads to the oligomerization of BAK/BAX, mitochondrial outer



membrane permeabilization (MOMP), and the release of cytochrome C, caspase activation and cell death (Youle and Strasser 2008).

The acquired resistance and evasion of apoptosis, which is central to therapeutic resistance, is an established hallmark of cancer (Hanahan and Weinberg 2011). MCL1 is integral to the resistance of apoptosis in a substantial number of solid and hematopoietic cancers, as supported by a wealth of genetic and functional data. Internal efforts have demonstrated that knockdown of MCL1 expression by siRNA induces cell death in multiple cancer cell lines.

Mouse knockout studies have implicated MCL1 in the maintenance of plasma cells, an observation that suggests MCL1 may be a critical pro-survival factor in multiple myeloma (Peperzak, Vikstrom et al. 2013).

The current data package is supportive of multiple myeloma as an initial study population. MCL1 also provides a useful target for the treatment of subjects with AML as it is essential for the development and sustained growth of AML. MCL1 dependency was detected in AML mouse models (Xiang et al. 2010) and in human AML-derived cell lines. It was shown that deletion of MCL1 but not loss or pharmacological blockade of BCL-XL, BCL-2 or BCL-W induced the death of transformed AML and cured the disease in AML-afflicted mice (Glaser, et al 2012). The upregulation of MCL1 has been described at the time of AML relapse (Kaufmann et al, 1998). In FLT3-ITD AML, upregulation of MCL1 is dependent on FLT3 signaling and an essential effector of FLT3-ITD-mediated drug resistance (Bose et al 2013). Targeting MCL1 sensitizes FLT3-ITD-positive leukemia to cytotoxic therapies (Kasper et al 2012).

# 2.3.1 Dose Selection Rationale

# 2.3.1.1 Starting and Maximum Planned Doses

The proposed AMG 397 doses are 80, 160, 320, and 640 mg. During dose escalation (Part 1), AMG 397 will be given once daily for 2 consecutive days followed by 5 days break and repeated each week for 4 weeks of treatment cycle. One treatment cycle is 28 days in length and includes 8 administrations of AMG 397.

For dose expansion (Part 2), AMG 397 will be given once daily for 2 consecutive days followed by 5 days break and repeated each week for 4 weeks of treatment cycle. One treatment cycle is 28 days in length and includes 8 administrations of AMG 397. The planned dose level(s) for dose expansion (MTD/RP2D) will be determined based on data collected during dose escalation.



The proposed clinical starting dose of 80 mg is based on the highest non-severely toxic dose (HNSTD) noted in a GLP toxicology study in beagle dogs. The HNSTD dose of 15 mg/kg/day in beagle dogs corresponds, per ICH S9 Guidance, to a human daily equivalent dose of 83 mg. AMG 397 human pharmacokinetics (PK) parameters were predicted from a combination of in vitro and in vivo nonclinical data. At the starting dose of 80 mg administered orally once daily for 2 consecutive days followed by 5 days break, the predicted exposure margins of maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) to the rat STD10 are 116-fold and 211-fold, respectively. The predicted exposure margins of Cmax and AUC to the dog HNSTD are estimated at 15-fold and 15-fold, respectively, at the starting dose administered orally once daily for 2 consecutive days break.

 Table 2. Predicted Human Exposures and Exposure Multiples at Steady-state

 After Oral Dosing of AMG 397

				Exposure	Margins	
Clinical Dose <sup>a</sup> Predicted Exposure <sup>b</sup>		AUC	0-96 <sup>C</sup>	Cm	ax <sup>C</sup>	
(mg)	AUC₀₋96 (hr⋅µg/mL) <sup>c</sup>	C <sub>max</sub> (μg/mL)	Rat 4-week	Dog 4-week	Rat 4-week	Dog 4-week
80	12.2	0.35	211	15	116	15
160	24.5	0.70	105	8	58	7
320	48.9	1.39	53	4	29	4
640	97.8	2.79	26	2	15	2

Approved

 $AUC_{0-96}$  = area under the concentration time curve from 0 to 96 hr;  $C_{max}$  = maximum observed concentration; HNSTD = highest non-severely toxic dose;  $STD_{10}$  = severely toxic dose in 10% of the animals.

<sup>a</sup> Once daily dosing for 2 consecutive days followed by 5 days break

<sup>b</sup> Human PK was simulated based on human body weight of 60 kg and height of 170 cm

<sup>c</sup> Rat day 22 exposure at 500 mg/kg (STD<sub>10</sub>): C<sub>max</sub> = 40.6 μg/mL, AUC = 2580 μg/mL·hr (Study 122859). Dog (male) day 15 exposure at 15 mg/kg (HNSTD): C<sub>max</sub> = 5.13 μg/mL, AUC = 186 μg/mL (Study 122859). Male value used because exposure was lower than in females.

The highest planned dose is 640 mg. Safety and tolerability data from prior dose levels will guide the dose escalations and the planned top dose for AMG 397 in the dose escalation phase. The maximum tolerated dose (MTD) identified from the dose escalation phase will inform the dose expansion phase. The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.



A safe and tolerable dose of AMG 397 will have evidence of anti-tumor activity in subjects with selected RR hematological malignancies as measured by Objective Response Rate (ORR).

# 3. EXPERIMENTAL PLAN

# 3.1 Study Design

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally in adult subjects with selected RR hematological malignancies.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

# Dose Escalation- Part 1

During dose escalation (Part 1), AMG 397 will be administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle.

Dose escalation will estimate MTDs for Group 1A and Group 1B using an adaptive, BLRM design. Table 3 shows the planned dose levels for dose escalation. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on any dose escalation/change. For more details regarding the dose escalation, please see Section 6.2.1.2

Dose Cohort Levels	Dose (mg) PO
1	80
2	160
3	320
4	640

Table 3. Planned Doses per Dose Cohort Level



Dose escalation for Group 1A and Group 1B will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 28 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.

Dose escalation for both Group 1A and 1B respectively, will continue until any of the following events:

- The highest planned dose level for each group is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

Intermediate doses and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data as decided by the DLRT.

#### Lead-in Dosing

Due to the potential risk of TLS for subjects affected by hematologic malignancies, it is anticipated that lead-in dosing may be implemented. At any point during the study, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. See Section 6.2.1.1.1 for more details

#### Dose Expansion – Part 2

Upon completing the dose escalation part of the study and depending on data obtained, dose expansion may proceed in groups with selected RR hematological malignancies below:

- Group 2A will consist of subjects with Multiple Myeloma (MM)
- Group 2B will consist of NHL subjects with Diffuse Large B-cell Lymphoma (DLBCL)
- Group 2C will consist of subjects with Acute Myeloid Leukemia (AML)



Dose expansion in all of these groups may take place concurrently. The maximum tolerated dose (MTD) for each indication, identified from the dose escalation phase, will inform the dose expansion phase.

## Intra-subject Dose Escalation

Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT and after consultation with the PI and sponsor as long as no DLT has been reported for this subject during or after completion of the DLT period.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

# 3.2 Number of Sites

This study will be conducted at up to 20 sites globally in Australia, Europe, Japan and the United States. Additional regions, countries, or sites may be added.

Sites that do not enroll subjects into an open cohort within 4 months of site initiation during dose escalation or expansion may be closed or replaced.

#### 3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects".

Up to 90 evaluable subjects will be enrolled in the study. Up to 60 evaluable subjects will be enrolled during dose escalation (up to 30 in both Groups 1A and 1B). Up to 30 evaluable subjects will be enrolled into the dose expansion part (up to 10 each for Groups 2A, 2B, and 2C). Based on emerging data, additional subjects may be enrolled.

The rationale for the number of subjects required is detailed in Section 10.3.

#### 3.4 Replacement of Subjects

During dose escalation, subject(s) may be replaced if:

- Subject(s) is not DLT-evaluable. See Section 6.2.1.2 for definition of DLT-evaluable
- Subject(s) discontinues treatment for any reason other than a DLT during the DLT-observation period

Additional subjects may also be enrolled if Amgen's medical monitor determines that the minimum required number(s) of evaluable subjects have not been enrolled in each cohort.



# 3.5 Estimated Study Duration

# 3.5.1 Study Duration for Subjects

The study duration for each subject is approximately 8 months consisting of up to 21 days in the screening period, approximately 6 months of treatment period, an EOT visit, and a SFU visit approximately 28 (+ 7) days after their last dose of AMG 397.

For dose expansion part only, long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397, for all subjects who have not withdrawn consent to assess for survival and/or the commencement of subsequent cancer therapy.

This study duration may vary depending on the subject's disease, ability to tolerate AMG 397 and/or willingness to participate in the study.

<u>End of study (EOS) for an individual subject:</u> The date when the subject completes the final protocol-specified procedure or SFU/LTFU visit whichever is later. This date will be recorded on the EOS electronic CRF (eCRF)

# 3.5.2 End of Study

**<u>Primary Completion</u>**: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

**End of Study**: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

#### 4.1 Inclusion Criteria

- 101. Subject has provided informed consent prior to initiation of any study-specific activities/procedures.
- 102. Age  $\geq$  18 years old



103. Pathologically-documented, definitively-diagnosed relapsed or refractory MM, NHL, or AML (Appendix G) and is intolerant to, or considered ineligible for available therapies known to provide clinical benefit.

#### 104. MM subjects only:

- Measurable disease per the IMWG response criteria (Appendix E; assessed within 21 days prior to enrollment), as indicated by one or more of the following:
  - Serum M-protein ≥ 0.5 g/dL
  - Urine M-protein ≥ 200 mg/24 hours
  - For Subjects who do not meet 1 of the 2 prior criteria:
    - Serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) AND an abnormal sFLC ratio (< 0.26 or > 1.65) as per the IMWG response criteria

#### 105. NHL subjects only:

• Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension

#### 106. AML subjects only:

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix H)
- More than 5% blasts in bone marrow

#### 107. MM and NHL subjects only:

- Hematological function, as follows without transfusion or growth factor support within 2 weeks prior to study day 1:
  - Absolute neutrophil count ≥ 1.0 X 10<sup>9</sup>/L
  - Hemoglobin > 8 g/dL
  - Platelet count ≥ 75 X 10<sup>9</sup>/L

**NOTE for MM subjects only:** Platelet count  $\ge$  50 X 10<sup>9</sup>/L (in subjects where

< 50% of bone marrow nucleated cells were plasma cells)  $OR \ge 30 \times 10^{9}/L$ 

(in subjects where  $\geq$ 50% of bone marrow nucleated cells were plasma cells) without transfusion or growth factor support are allowed into the study.

- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (Appendix F)
- 109. Life expectancy of > 3 months, based on the opinion of the investigator
- 110. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption



- 111. Hepatic function, as follows:
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
     < 3 x upper limit of normal (ULN)</li>
  - Total bilirubin (TBIL) < 1.5 X ULN (except subjects with Gilbert's syndrome)</li>
- 112. Cardiac function, as follows:
  - Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an ECHO or MUGA
  - No clinically significant ECG findings.
- 113. Renal function as follows:
  - Calculated or measured creatinine clearance (CrCl) of ≥ 30 mL/minute calculated using the formula of Cockcroft and Gault [(140 Age) × Mass (kg) / (72 × serum creatinine mg/dL)]. Multiply result by 0.85 if female.

#### Additional criteria for Part 2 - Dose Expansion subjects

#### 114. MM subjects only

• Pathologically documented, definitively diagnosed, relapsed or refractory disease following at least 3 lines of therapy including but not limited to a proteasome inhibitor, an immunomodulatory agent and/or CD38-targeted immunochemotherapy.

**NOTE:** The investigator must be of the opinion that no other treatment option will

result in a durable response.

#### 115. NHL subjects only

• Pathologically confirmed DLBCL that has demonstrated clinical or radiographic progression on at least two prior therapies

NOTE: For subjects with refractory disease and who have received radiotherapy,

PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy.

#### 116. AML subjects only

 Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix H) persisting or recurring following no more than 2 lines of prior therapies

#### 4.2 Exclusion Criteria

- 201. Previously received an allogeneic stem cell transplant within 6 months of study day 1 OR having signs or symptoms of acute or chronic graft-versus-host disease
- 202. Autologous stem cell transplant < 90 days prior to study day 1
- 203. Candidates for stem cell transplant should have failed or are not considered eligible for either allogeneic and autologous transplant



204. History of other malignancy except:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- 205. Myocardial infarction within 6 months of study day 1
- 206. Symptomatic congestive heart failure (New York Heart Association > Class II) (Appendix F)
- 207. History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past6 months prior to study day 1
- 208. Uncontrolled active infection requiring intravenous anti-infective treatments within1 week of study day 1
- 209. Known positive results for human immunodeficiency virus (HIV)
- 210. Active hepatitis B and C based on the following results:
  - Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
  - Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
  - Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C
- 211. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 1, or to levels dictated in the eligibility criteria with the exception of grade 2 peripheral neuropathy, alopecia or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 4 weeks prior to study day 1 may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor)
- 212. Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures) within 14 days of day 1.
- 213. Prior systemic radiation therapy must have been completed at least 28 days before study day 1. Prior focal radiotherapy completed at 14 days before study day 1.



214. Males and females of reproductive potential who are unwilling to practice an acceptable method(s) of effective birth control while on study through 3 months after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap, or cervical sponge), hormonal birth control or IUD (females).

**NOTE:** A woman is considered of childbearing potential (WOCBP), (ie, fertile) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- 215. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 3 months after receiving the last dose of study drug.
- 216. Females with a positive pregnancy test or planning to become pregnant while on study through 3 months after receiving the last dose of study drug.
- 217. Males who are unwilling to abstain from sperm donation while on study through3 months after receiving the last dose of study drug.
- 218. History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
- 219. Use of any over-the-counter or prescription medications within 14 days or 5 half-lives (whichever is longer), prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- 220. Use of herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within 14 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- 221. Use of any known inhibitors of P-gp within 14 days or 5 half-lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- 222. Use of known cytochrome P450 (CYP) 3A4 sensitive substrates, (with a narrow therapeutic window), within 14 days or 5 half-lives (whichever is longer) of the drug or its major active metabolite, whichever is longer, prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor



- 223. Use of known P-gp substrates (**with a narrow therapeutic window**) within 14 days or 5 half-lives (whichever is longer) prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- 224. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, long term follow-up) to the best of the subject and investigator's knowledge
- 225. Known sensitivity to any of the products or component to be administered during dosing

#### 226. MM subjects with any of the following criteria are excluded:

- Multiple myeloma with IgM subtype
- POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
- Existing plasma cell leukemia
- Waldenstrom's macroglobulinemia
- Amyloidosis

#### 227. NHL subjects with the following criteria are excluded:

- CNS lymphoma or evidence of uncontrolled CNS disease
- Burkitt's lymphoma
- Lymphoblastic lymphoma

#### 228. AML subjects with any of the following criteria are excluded:

- Circulating white blood cells > 25,000 /µl. Hydroxyurea to control peripheral blood leukemic cell counts, within 24 hours of study day 1 is permitted.
- Promyelocitic leukemia

#### 5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when they have met all eligibility criteria, including completing any pre-treatment safety assessment(s) prior to initial dosing on day 1. The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment eCRF.



An Amgen representative will notify the sites in writing when a cohort is open to screen new subjects. Each subject who enters into the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The unique number will consist of 11 digits: digits 1 to 3 represent the last 3 digits of the protocol (eg, 173), digits 4 to 8 the country code and site number, digits 9 to 11 the subject number at the site.

Subjects who fail to meet the eligibility criteria will be allowed to rescreen once with agreement between the Amgen Medical Monitor and PI. Re-screened subjects must perform all qualifying assessments required for eligibility, including reconsenting the subject, within 21 days of their D1 visit. The subject identification number, assigned during the original screening period must remain constant throughout the entire clinical study if a subject is rescreened.

#### 5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a dose cohort/group (dose escalation part) or the dose expansion part, respectively, are open to screen and enroll new subjects. The notification will include the cohort/group and dose level in which subjects will be enrolled. The treatment assignment date is to be documented in the subject's medical record and on the enrollment eCRF.

#### 6. TREATMENT PROCEDURES

#### 6.1 Classification of Product

The Amgen Investigational Product used in this study is AMG 397.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 397.

#### 6.2 Investigational Product

#### 6.2.1 Amgen Investigational Product AMG 397

AMG 397 is an oral MCL1 inhibiting agent. AMG 397 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 397 will be provided as 5 mg, 20 mg, and 100 mg tablets, and will be packaged in bottles of 15 tablets.



AMG 397 will be dispensed and administered at the research facility by qualified staff member(s).

#### 6.2.1.1 Dosage, Administration, and Schedule

During dose escalation (Part 1), AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. Table 3 shows the planned dose levels for dose escalation.

During dose expansion (Part 2) AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.

On days of hospitalization and during clinic visits, doses will be administered at the clinic. Subjects will self-administer AMG 397 on all other designated timepoints per Table 4 and Table 5 on days without clinic visits.

AMG 397 can be taken with or without food (ie, subjects may choose to eat prior to or after taking study drug). The tablet should be swallowed whole without crushing or breaking. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Subjects will be asked to record the date, time, and number of tablets consumed in a subject drug diary that must be brought to each study visit and will be reviewed by study staff. The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).

The amount dispensed, amount returned, date dispensed, date returned, and lot number of AMG 397 are to be recorded in the site's drug accountability log for each subject. Please refer to the Investigational Product Instructional Manual for more details on dosage, administration and schedule of AMG 397.

If a subject develops a reaction, subjects should acutely be treated according to best clinical practice. Medication may be administered as deemed appropriate by the investigator to control any reactions according to best clinical practice. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. All medication and symptoms should be documented in the eCRF. Amgen must be notified within 24 hours when a subject has had  $\geq$  Grade 3 AE.

The effects of overdose of this product are not known.



#### 6.2.1.1.1 Lead-in Dosing

There is a potential for tumor lysis syndrome (TLS) in subjects affected by hematologic malignancies especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS, tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to any dose escalation (Section 6.5.7).

Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.

The DLRT will convene to review the safety data and may determine a lead-in dose, which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

**NOTE:** Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Once lead-in dosing is initiated, additional monitoring of electrolyte values is required prior to dosing at the following times (see Table 4 and Table 5):

- Prior to the Week 1, Day 1 Dose
- Prior to each dose during the Lead-in Period
- Prior to the initial dosing at the target dose level

Prior to administering AMG 397, all electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be within normal range.

**NOTE:** Laboratory value changes must be confirmed by another laboratory test (1-2 hours later) prior to assigning a TLS grade.

#### Dose Adjustments for Lead-In Dosing

Evidence of TLS will be carefully monitored on study and AMG 397 will be held until resolution of TLS abnormalities. Following lead-in dosing of AMG 397, if one or more



Cairo-Bishop criteria is met (See Appendix K and Appendix L), no additional AMG 397 doses will be administered until it is resolved (eg, laboratory values are no longer within range of the values stated in Appendix K and Appendix L). Upon resolution, the subject will repeat the lead-in dosing for an additional week prior to receiving the target dose.

**NOTE:** Lead-in dosing will be repeated if the subject is observed to meet one or more of the Cairo-Bishop criteria post-dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

#### 6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The Dose Level Review Team (DLRT) will convene before decisions to dose escalate or de-escalate is made or when cohorts are suspended per protocol. The DLRT will be composed of select Investigator(s), Amgen medical monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager (CRSM) and Biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacologist). The DLRT voting members include the Amgen Medical Monitor and Global Safety Officer or designee, in consultation with the investigator(s) or designee. The DLRT members are responsible for dosing decisions, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; implementation of lead-in dosing, or determination of RP2D. See Section 3.1 for more details regarding the study design and the dose escalation plan for this study.

The DLT-observation period is defined as, at minimum, 28 days after the initial dose of AMG 397. Once lead-in dosing period is initiated, the DLT-observation period is defined as the amount of time for subject(s) for each dose cohort to receive at least 1 week of lead-in dose and 3 weeks of target dose.

A subject is deemed DLT-evaluable if during the DLT-observation period the subject met at least one of the following criteria:

- Received at least 75% of the planned dose of AMG 397
- Experienced a DLT

Available study data, including data collected after the initial DLT-observation period along with demographics, IP administration, medical history, concomitant medications,

adverse events (AE), ECG, vital signs, laboratory results and PK/PD information will be reviewed. In addition to DLTs, all  $\geq$  grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity described by Appendix D. An Amgen representative will notify the sites in writing the dosing decision from the DLRM and when a cohort is open to screen new subjects.

DLTs experienced by subjects after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity.

Dose escalation for each group will continue until any of the following events occur:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

If there are concerns about the tolerability of the current dosing schedule, alternative dosing schedules or lower dose(s) may be explored, including modification of the lead-in period dosing regimen. The alternative dose and schedule will be jointly determined by the investigators and the Amgen medical monitor, based on pharmacokinetic and safety and toxicity data.

#### 6.2.1.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

NOTE: For subjects who meet clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) see Section 6.2.1.1.1 for dose adjustment details.

#### **Dosage Adjustments**

The subject should continue on the same dose of AMG 397 throughout the study unless the following events occur:

- For subjects experiencing an adverse event meeting the DLT definition or intolerable related adverse events BUT showing evidence of response, there will be an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose escalation part of the study.
- AMG 397 can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 397 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.



**NOTE:** Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction.

Subjects should not be re-challenged with AMG 397 if the following AMG 397-related adverse events occur:

- Any life-threatening adverse events
- DILI (Drug Induced Liver Injury) meeting Hy's law
- Persistent grade 3 adverse events that do not recover to baseline or Grade 1 within 4 weeks of last dose
- Any treatment-related adverse event meeting DLT-criteria that recurs

#### Dosage Delays

The investigator should inform the Amgen Clinical team as soon as the unexpected

dosage delay occurs. The following dosage delay rules apply:

- If the dosing delay is ≤ 3 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator.
- If the dosing delay is more than 4 weeks (missing 1 cycle):
  - Due to treatment related AEs, the subject will be removed from the study.
  - Due to other conditions other than treatment related AEs, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 397 treatment.

#### Rules for Dose Withholding

AMG 397 should be withheld for any of the following:

- Suspected DLT (including AEs that meet DLT definition outside DLT-observation period)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 x ULN or total bilirubin greater than 1.5 x ULN

#### Rules for Restarting

AMG 397 dosing can be resumed:

- If the toxicities resolve to grade  $\leq 1$  or return to subjects' baseline values
- Restarting of therapy is deemed safe by the investigators and Amgen's medical monitor.



#### **Rules for Permanent Discontinuation**

Subjects will permanently discontinue from the investigational product if:

- Subjects experience adverse events meeting the DLT criteria at any time. Subjects will be followed until the DLT is resolved, returns to baseline value or is considered stable. Subjects will be withdrawn from AMG 397 treatment and will be treated as deemed appropriate by the investigator or treating physician. Except for:
  - Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 397, may have the option to continue therapy once the adverse events recover to baseline or Grade 1 and the re-introduction of AMG 397 is deemed safe by the investigator, Amgen's medical monitor, and Global Safety Officer. The subject should restart at a reduced dose.
  - Subjects who experience TLS as detail, see Section 6.2.1.1.1 for dosing details.
- Intolerability of the study treatment
- The dosing is delayed > 4 weeks due to AMG 397-related adverse events
- Disease progression according to IMWG (MM), Lugano classification (NHL), or 2017 ELN response criteria (AML) and/or per institutional guidelines as applicable
- Clinical significant deterioration of health status
- Withdrawal of informed consent
- Subject becomes pregnant or is breastfeeding
- Initiation of new systemic anti-cancer therapy not provided in this study
- Study is terminated by the sponsor.

#### 6.2.1.4 Dose Stopping Rules

Please refer to Section 10.4 for dose stopping rules.

#### 6.3 Other Protocol Required Therapies

#### 6.3.1 Pre-dosing requirements for AMG 397

To mitigate risk of TLS, all subjects are to receive TLS prophylaxis prior to first dose of AMG 397 and prior to any dose escalation. Refer to Section 6.5.7 for specific requirements.

#### 6.4 Dose Limiting Toxicities

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Determination of the severity of adverse events will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

#### For MM and NHL subjects only:

A DLT is defined as a treatment-related AE(s), that occur during the DLT-observation period (see Section 6.2.1.2) including any:

- ≥ Grade 3 non-hematological AE's **EXCEPT**:
  - $\circ \geq$  Grade 3 fatigue if <7 days
  - Grade 3 nausea, vomiting and/or diarrhea if < 3 days and controlled with medical management
  - Laboratory parameters of grade ≥ 3 that improve with medical management to grade ≤ 2 within 3 days
- $\geq$  Grade 4 hematologic AE's AND:
  - $\circ \geq$  Grade 3 neutropenia with fever
  - $\circ$   $\geq$  Grade 3 thrombocytopenia with Grade  $\geq$  2 hemorrhage
  - $\circ \geq$  Grade 3 anemia with symptoms requiring intervention (eg, transfusion)

NOTE: ≥ Grade 4 neutropenia must be lasting > 7 days

• Any grade 5 AE that is not clearly due to disease progression

#### For AML subjects only:

Due to the nature of AML, hematologic adverse events will not be considered DLTs.

However, prolonged pancytopenia in the presence of a hypocellular bone marrow

(ie, cellularity 5% or less without evidence of leukemia) that lasts longer than 42 days will be considered dose-limiting myelosuppression.

#### Non-hematological toxicity:

- ≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support
- ≥ Grade 3 fatigue persisting > 7 days
- Any other  $\geq$  Grade 3 adverse event
- Failure to recover from AMG 397 related toxicities to grade ≤ 1 or baseline severity after delaying next cycle up to 14 days

#### For all subjects:

• Any Clinical TLS (refer to Appendix K)

If a DLT of TLS is observed during the lead-in period, it will be attributed to the lead-in period and a modification may be made to the lead-in period regimen for subsequent cohorts. Any other DLTs observed during the lead-in and/or designated cohort dosing period may require a modification of the designated cohort dose (and/or lead-in period regimen, if appropriate) as directed per the Dose Escalation Guidelines.



Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin level (TBL) of > 2x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 6.7 for hepatotoxicity management and Appendix A for further explanation of Hy's law case and Management of Hepatic Function). Grade 3 or 4 elevation of serum lipase without clinical signs or symptoms of pancreatitis.

#### 6.5 Potential Risk Management Guidelines for AMG 397

#### 6.5.1 Gastrointestinal Toxicity

Evidence of gastrointestinal toxicity will be monitored in the FIH study through clinical evaluations, safety laboratory tests, stopping rules, and associated adverse events.

Management should be tailored to the appropriate treatment according to the local standard of care and institutional guidelines.

#### 6.5.2 Bone Marrow Toxicity

Monitoring of vital signs, hematology parameters and associated adverse events will be conducted in the FIH study. Specific eligibility criteria, stopping rules and dose-hold rules, pertaining to hematology parameters, are provided in Section 6.2.1.3.

#### 6.5.3 Reproductive Toxicity- Male

Men of reproductive potential who are unwilling to practice an acceptable method of effective birth control will be excluded from the study. See section 4.2 for list of acceptable methods of effective birth control.

#### 6.5.4 Drug-drug interactions

A list of prohibited drugs as well as subject exclusion criteria are included in the protocol. Subjects receiving any of the drugs cited in the exclusion criteria and/or prohibited drugs as listed in the FIH protocol will be excluded from this study. Caution should be exercised when administering AMG 397 with drugs that have a narrow therapeutic window and prescribing information that includes contraindications, warnings or precautions related to their use with known inhibitors of CYP34A and P-gp.

#### 6.5.5 Hepatobiliary Toxicity

Evidence of hepatobiliary toxicity will be monitored as outlined in the study protocol through clinical evaluations, safety laboratory tests, stopping rules, and associated adverse events.



Adverse events associated with cardiac function will be monitored through blood pressure, heart rate, echocardiogram, and ECG measurements. Subsequent withholding rules, as outlined in the study protocol, will be followed.

#### 6.5.7 Tumor Lysis Syndrome (TLS)

#### Prophylaxis and Management of TLS

Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to every dose escalation.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-

disciplinary management will be conducted per institutional protocols

(Coiffier et al, 2008; Cairo et al, 2004).

- Initiate allopurinol or equivalent to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase may be used per PI discretion. Dosing per institutional guidelines.
- All subjects will be hospitalized for intensive monitoring:
  - For the first 2 doses received, beginning 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
  - Once lead-in dosing is initiated (see Section 6.2.1.1.1):
    - For the first 2 doses received (Lead-in dosing), beginning at least 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
    - Each time an additional week of lead-in dosing is instituted (Section 6.2.1.1.1)
    - For the first 2 doses received after the dose is escalated (target dose) beginning at least 24 hours prior to dosing day (usually day 7) until 24 hours post the second dose
- During hospitalization, intensive safety laboratory monitoring per designated timepoints per Table 4 and/or Table 5 to identify and prompt management of any metabolic changes.
  - Pre-treatment serum chemistry and hematology laboratory samples must be drawn within 24 hours prior to first dose, and electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be reviewed and within normal range prior to AMG 397 dosing. The investigator's decision to proceed with AMG 397 treatment initiation may be based on these laboratory values. These labs must be reviewed in real time by the investigator.

**NOTE:** If the potassium, uric acid, inorganic phosphate and/or creatinine values are higher than the normal range or the calcium is lower or higher than the normal range, dosing can be resumed following review of



laboratory values and agreement between the Amgen medical monitor and investigator.

- Prophylactic reductions of potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended per PI discretion.
- Day 2 dosing of AMG 397 should not be administered until the 24 hours post-dose laboratory values are reviewed by the investigator.
- All 24-hour laboratory assessments may be taken ± 2 hours, if necessary.
- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria (Appendix L) are met, no additional AMG 397 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.
- Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared.
- Management recommendations of laboratory abnormalities as stated below:



Abnormality	Management Recommendations <sup>1,2</sup>
Hyperkalemia (including rapidly ris	-
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	<ul> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still &lt; upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour.</li> <li>Resume per protocol testing if change in potassium is &lt; 0.2 mmol/L, and potassium &lt; ULN, and no other evidence of tumor lysis.</li> <li>At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.</li> </ul>
Potassium > upper limit of normal	<ul> <li>Perform STAT ECG and commence telemetry.</li> <li>Nephrology notification with consideration of initiating dialysis.</li> <li>Administer Kayexalate 60 g (or Resonium A 60 g).</li> <li>Administer furosemide 20 mg IV × 1.</li> <li>Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If potassium &lt; ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.</li> </ul>

Abnormality	Management Recommendations <sup>1,2</sup>
Hyperkalemia (including rapidly ris	sing potassium) (continued)
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	<ul> <li>Perform STAT ECG and commence telemetry.</li> <li>Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis.</li> <li>Administer Kayexalate 60 g (or Resonium A 60 g).</li> <li>Administer furosemide 20 mg IV × 1.</li> <li>Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV.</li> <li>Administer sodium bicarbonate 1 to 2 mEq/kg IV push.</li> <li>If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.</li> </ul>
Hyperuricemia	creating every hour STAT.
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	<ul> <li>Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes).</li> <li>If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> </ul>
Uric acid $\geq$ 10 mg/dL (595 µmol/L) Uric acid $\geq$ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase $\geq$ 0.3 mg/dL ( $\geq$ 0.027 mmol/L) from pre-dose level	<ul> <li>Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes).</li> <li>When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Consult nephrology (or other acute dialysis service).</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If uric acid &lt; 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> </ul>

Abnormality	Management Recommendations <sup>1,2</sup>
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) <u>AND</u> Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	<ul> <li>Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring.</li> <li>Telemetry.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> <li>Calculate corrected calcium and check ionized calcium if albumin low.</li> </ul>
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	<ul> <li>Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).</li> <li>Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL).</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If phosphorus &lt; 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> </ul>
Creatinine	
Increase $\geq 25\%$ from baseline	<ul> <li>Start or increase rate of IV fluids.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.</li> </ul>

### 6.6 Support Care Guidelines for AMG 397

#### 6.6.1 Management of Infections

Subjects with evidence of existing infection should be closely monitored while being treated with AMG 397. Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 397 until infection per exclusion criteria in Section 4.2. Management should be tailored to the appropriate prophylaxis and/or treatment for the underlying infection according to the local standard of care and institutional guidelines.

Subjects who may experience neutropenia are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial (treatment with ciprofloxacin) and antifungal (treatment with posaconazole).

These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification. Subjects experiencing diarrhea should be closely monitored for their electrolyte levels.

#### 6.6.2 Management of Renal Toxicities

Renal dysfunction is one of the multiple myeloma-related organ/tissue dysfunction. Renal function must be monitored closely during treatment with AMG 397. Serum chemistry values, including BUN, serum creatinine, and urine for urinalysis and microscopic exam (microscopic exam only needed for positive dipstick), must be obtained per the schedule of assessments (see Table 4). Management should be tailored to the appropriate treatment for the underlying renal disorder according to the local standard of care and institutional guidelines.

#### 6.7 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL]) or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product. Withholding is either permanent or conditional depending upon the clinical circumstances discussed below (as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

# 6.7.1 Criteria for Permanent Withholding of AMG 397 due to Potential Hepatotoxicity

AMG 397 should be permanently withheld and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

• Increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

AND

• TBIL > 2x upper limit of normal (ULN) or INR > 1.5

#### AND

- No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:
  - Hepatobilliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella, Toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms,
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

## 6.7.2 Criteria for Conditional Withholding of AMG 397 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 397 outlined above and have no underlying liver disease and eligibility criteria requiring normal transaminases and TBIL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for $\ge$ 2 weeks
Any Any	<ul> <li>&gt; 5x ULN but &lt; 8x ULN and unable to adhere to enhanced monitoring schedule</li> <li>&gt; 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice.</li> </ul>

Elevation of either AST or ALT according to the following schedule:

- OR: TBIL > 3x ULN at any time
- OR: ALP > 8x ULN at any time



AMG 397 should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject should be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBIL, is discovered and the laboratory abnormalities resolve to normal or baseline.

## 6.7.3 Criteria for Rechallenge of AMG 397 After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then AMG 397 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1.3) should not be rechallenged. If signs or symptoms recur with rechallenge, then AMG 397 should be permanently discontinued.

#### 6.8 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.10

Concomitant therapies are to be collected from screening start through the EOS visit. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications, transfusions and fluids.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, G-CSF and other care as deemed appropriate, and in accordance with their institutional guidelines. For subjects with AML hydroxyurea for 7 days at a dose of 1 - 10 g/day is allowed prior to the first cycle of AMG 397 treatment for subjects with high WBC (> 25,000 cells/ul) and during the first cycle but not on dosing days at a dose of up to 5 g/day.

For all concomitant medication collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

#### 6.9 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or



clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or

non-investigational product(s) or device(s) supplied by Amgen are to be reported

according to the instructions provided in the IPIM.

#### 6.10 Excluded Treatments and Procedures During Study Period

The following medications and/or therapies should not be administered during the study:

- Allogeneic stem cell transplant
- Autologous stem cell transplant
- Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures)
- Systemic or focal radiotherapy
- Over-the-counter medication(s) that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- Any known inhibitors of P-gp or grapefruit juice or grapefruit containing products that were not reviewed and approved by the principal investigator and the Amgen medical monitor
- Herbal medicines (eg, St. John's wort), vitamins, and supplements that were not reviewed and approved by the principal investigator and the Amgen medical monitor
- Any known cytochrome P450 (CYP) 3A4 sensitive substrates, with a narrow therapeutic window, that were not reviewed and approved by the principal investigator and the Amgen medical monitor

If use of any other prior or concomitant medication or procedure is in question, please refer to prescribing information and/or consult with Amgen Medical Team.

#### 7. STUDY PROCEDURES

#### 7.1 Schedule of Assessments

Please refer to Table 4 for Schedule of Assessments.

Once lead-in dosing is initiated follow Table 5 for Cycle 1 only. For all subsequent cycles and study periods follow Table 4.

	S															TR	EA	ГМЕ	NT															
CYCLE(S)	SCREENING														1														2		Every cycle from 3 & beyond		SAFETY	
WEEK(S)	ING											1											2			3		1	2	3	1	EOT		
DAY(S)	-21 to -2	-1					1							:	2				3	4			8			15	22	1	8	15	1	т	FOLLOW-UP	(26)
HOUR(S) (relative to time of dosing)			Pre- dose		1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose		0	2	3	5		Pre	dos	e unlo	ess sj	pecified		Ę	
Informed consent	х																																	
Clinical evaluation (1)	х	х	х								х								х	Х	х					х	х	х	х	х	х	х	х	1
Vital signs (T, BP, HR, RR)	х	х	х				х	х	х	х	х				х	х	х	х	х	Х	х					х	х	х	х	х	х	х	х	
12-lead ECG (2)	Х	Х	Х		Х	Х	Х	Х	Х	Х	Х		Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
Echocardiogram or MUGA	х																															х		
Hospitalization (3)			-																															
TLS prophylaxis (4)		х																																
AMG 397 Dosing (5)				x								х										x				for 5 c	2 co lays	nsec brea	utive k at a	days weel	y once daily followed by dy interval, tment cycle			
Dosing diary review (5)											х								х		х					х		X	х	X	х	х		
AE Reporting					•																													•
SAE Reporting		-	•		•																													
Prior /concomitant medication(s)	-																																	-

#### Table 4. Schedule of Assessments

Footnotes are defined at the end of Table 5



Page 60 of 130

	SC														TF	REA	TME	INT															
CYCLE(S)	SCREENING													1														2		Every cyc from 3 & beyond		SAFE	
WEEK(S)	ING										1											2			3		1	2	3	1	ЕОТ	TYFO	LTFU (26)
DAY(S)	-21 to -2	-1				1								2				3	4			8			15	22	1	8	15	1	- 4	SAFETY FOLLOW-UP	(26)
HOUR(S) (relative to time of dosing)			Pre- dose	1	2	3	5	8	12	Pre- dos	0	1	2	3	5	8	12			r Pre	e 0	2	3	5		Pre	-dose	unle	ess sp	ecified		P	
Survival/Subsequen t anti-cancer therapy (6)																																	x
												L	AB	AS	SES	SM	EN.	TS															
AMG 397 PK (7)			х	х	х	х	х	х	х	х		х	х	х	х	х	х	х	х	х		Х	Х	Х							х		
CBC with diff (8)	х	х	х							х								Х	х	х					х	х	х	х	х	Х	х	х	
Chemistry (9)	х	х	х			х		х	х	х				х		х	х	х	х	х					х	х	х	х	х	Х	х	х	
Coagulation	х	х	х							х								х	х	х					х	х	х	х	х	Х	х	х	
Pregnancy test (10)	х		х																								х			х	х		
Urine sample collection (11)	х		х					х		х						х	I			х				х			х			х			
Hepatitis serology, HIV	х																	1															<u>.</u>

#### Table 4. Schedule of Assessments

Footnotes are defined at the end of Table 5



Page 2 of 4

Page 61 of 130

	s															TF	REAT	ГМЕ	NT															
CYCLE(S)	SCREENING														1														2		Every cy from 3 beyon	&	SAFE	
WEEK(S)	ING											1											2			3		1	2	3	1	EOT	TY FO	LTFU (26)
DAY(S)	-21 to -2	-1					1							:	2				3	4			8			15	22	1	8	15	1	7	SAFETY FOLLOW-UP	(26)
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5		Pre	-dose	unle	ess sp	pecified			
		•								BI	OM/	ARK	ER	and	d DI	SE/	ASE	AS	SES	SM	EN.	ΓS												
Bone marrow aspirate (12)	x					Γ	Γ																											Т
Whole blood Na/Hep (13)			х				x	х			х																							
Whole blood Cytochex (14)			х								х								х	Х	х													
Plasma	х																																	
Serum	х																																	
Cell Pellet	х																																	
	ONL	Y																																
SPEP/UPEP/ Immunofixation (15)	х																											х			Х	Х		Τ
SFLC (16)	х																											Х			Х	х		
Beta-2 microglobulin	х																															х		
Quantitative Ig (17)	х																															х		

#### Table 4. Schedule of Assessments

Footnotes are defined at the end of Table 5



	SC															TF	REA.	ГМЕ	NT														
CYCLE(S)	SCREENING														1														2		Every cycl from 3 & beyond		SAFET
NEEK(S)	ดิ											1											2			3		1	2	3	1	Ē	۲.
DAY(S)	-21 to -2	-1					1							:	2				3	4			8			15	22	1	8	15	1	EOT	SAFETY FOLLOW-UP
HOUR(S) (relative to time of dosing)			Pre- dose	• 0	1	2	3	5	8	12	Pre- dose		1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Pre	0	2	3	5		Pre	-dose	unle	ess sp	pecified		UP
Bone marrow biopsy	х																																
Bone marrow aspirate (18)																- Rep	eat c	ollec	tion i	n case	of C	R											
Plasmacytoma (19)	х																																
Skeletal survey (20)	х																																
NHL SUBJECTS	ONI	Y																															
_ymph Node Biopsy	х																																
Whole blood blasma Dose expansion only) (21)	x																											х			X (21)	x	
Bone marrow biopsy (22)	х																																
PET-CT and CECT maging (23)	х																											х			X (23)	х	
MRI Brain (24)	х																																
AML SUBJECTS	ON	ĹΥ	•																														
3one marrow aspirate (25)																												х			X (25)	x	
																																	ge 4

#### Table 4. Schedule of Assessments

Footnotes are defined at the end of Table 5



Page 63 of 130

CONFIDENTIAL

CYCLE																					C	CLE	1 01	NLY																	
DAY(S)	- 21 to -2	-1					1							2	2				3	4	7					8							ç	•				10	11	15	22
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	after D2	48h after D2 dose		Pre- dose	0	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	after D9	48h after D9 dose		
Informed consent	х																																								
Clinical evaluation (1)	х	х	Х								х								Х	х	х	х								Х								Х	х	х	х
Vital signs (T, BP, HR, RR)	х	х	Х				х	х	х	х	х				х	х	х	Х	х	х	х					х	х	х	х	Х				х	х	х	х	х	х	х	Х
12-lead ECG (2)	х	х	X (2)		х	х	х	х	х	х	х		х	х	х	х	х	Х	х	х	х			х	х	х	х	х	х	Х		х	х	х	х	х	х	х	х	х	>
Echocardiogram or MUGA	х																																								
Hospitalization (3)		•															→					-																			
TLS prophylaxis (4)		Х																			Х																				
AMG 397 dosing (5)				х								х											Х								х								)	(5)	
Dosing diary review (5)											х										х																	Х		х	Х
AE Reporting							<																															•			
SAE Reporting	1		-																																			-			
Prior /concomitant medication(s)																																						•			

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined at the end of Table 5

Page 1 of 4



|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | СҮ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | CLE                                                     | 1 01                                                    | ILY                                                     |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|------------
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----	-------------	-------------	--------------	-------------	------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
- 21 to -2	-1		•			1	
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                         |                                                         |                                                         | 1          | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            | 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              | 10                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                     |                                                                 | Pre-<br>dose                                                                                                                                                                                                                                                                                                                                                                          | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Pre<br>dos                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -<br>e 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 12 <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | fter<br>D2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | after<br>D2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Pre-<br>dose                                            | 0                                                       | 1                                                       | 2          | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 5  | 8           | 12          | Pre-<br>dose | 0           | 1          | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 5          | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | D9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | L                                                                                                                                                                                                                                                                                                                                                                                                                                                       | AB .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ASS                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | SES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | | | | | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             | 1          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | х                                                       |                                                         | х                                                       | х          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х  | х           | х           | х            |             | х          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                    | х                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   | х                                                               | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | х                                                       |                                                         |                                                         |            | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             | Х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | >                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   | x                                                               | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | >                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | ( X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                         | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | х                                                       |                                                         |                                                         |            | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    | х           | х           | Х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                    | х                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | >                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   | x                                                               | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | х                                                       |                                                         |                                                         |            | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             | Х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | _                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | х                                                       |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    | Х           |             | х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                    | <u> </u>                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | BIC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | OMA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | RK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ER                                                                                                                                                                                                                                                                                                                                                                                                                                                      | and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | d DI                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | SE/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | ASE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | E A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | SSE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | SS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ME                                                      | NTS                                                     | S                                                       |            | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| x                   | Γ                                                               |                                                                                                                                                                                                                                                                                                                                                                                       | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Т                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Τ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Т                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Τ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Γ                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Π                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Γ  |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    | Γ                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | х                                                       |                                                         |                                                         |            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х  |             |             | х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | х                                                       |                                                         |                                                         |            | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             | х            |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |                                                         |                                                         |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |             |             |              |             |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                    | 1                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     | to<br>-2<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X | to       -1         -2       -2         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X         X       X | to         -1           -2         Pre-dose           -1         Pre-dose           -2         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X | to         -1           -2         -1           -2         -1           Pre-dose         0           X         X         X           X         X         X         X           X         X         X         X           X         X         X         X           X         X         X         X           X         X         X         X           X         X         X         X           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         X         I           X         I         I         I           X         I <thi< th=""> <thi< th=""> <thi< th="">  &lt;</thi<></thi<></thi<> | to       -1         -2       Pre-<br>dose       0       1         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       I         X       X       X       X       I         X       X       X       X       I         X       X       X       X       I         X       I       I       I         X       I       I       I         X       I       I       I         X       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I <thi< th="">         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       <thi< th=""> <thi< th=""> <thi< th=""></thi<></thi<></thi<></thi<> | to       -1         -2       Pre-dose       0       1       2         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       X       X         X       X       X       X | to       -1       Image: respect to the symbol independent indep | to       -1       Pre-dose       0       1       2       3       5 $2$ $3$ $3$ $3$ $3$ $3$ $5$ $2$ $3$ $3$ $3$ $3$ $3$ $5$ $3$ $3$ $3$ $3$ $3$ $3$ $5$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $5$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $5$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ <td>to       -1       Image: rest and transformed and transforme</td> <td>to       -1       Image: descent independence independence</td> <td>to       <math>-1</math>      &lt;</td> <td>to       <math>^{-1}</math> <math>^{-1}</math></td> <td>to       <math>-1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>Pre-dose</math> <math>0</math> <math>1</math> <math>3</math> <math>3</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>Pre-dose</math> <math>0</math> <math>1</math> <math>3</math> <math>3</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>Pre-dose</math> <math>0</math> <math>1</math> <math>3</math> <math>3</math></td> <td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td> <td>to       -1       Image: relation of the stress of</td> <td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td> <td>to       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3       5       8         Image: Constraint of the constraint</td> <td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       11       2       3       5       8       12       2       2       3       5       8       12       2       2       11       11       11       11       11       11       11       11       11       11       11       11       11</td><td>to       1       <math>\cdot</math> <math>\cdot</math>&lt;</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>to       1                                                                                                              </td><td>21       1       1       1       2       3       4       7         2       1       1       2       3       5       8       12       Pre-dose       0       1       2       3       4       7         1       Pre-dose       0       1       2       3       5       8       12       Pre-dose       0       1       2         1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th< td=""><td>21                                               </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>21       1      </td><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>21       1       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -</td><td>21       1                                </td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>21       1       1       1       1       1       1       1       2       3       4       7       3       4       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></th<></td></t<></td> | to       -1       Image: rest and transformed and transforme | to       -1       Image: descent independence | to $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-1$ < | to $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ $^{-1}$ | to $-1$ $1$ $1$ $2$ $3$ $5$ $8$ $12$ $Pre-dose$ $0$ $1$ $3$ $3$ $3$ $5$ $8$ $12$ $Pre-dose$ $0$ $1$ $3$ $3$ $3$ $5$ $8$ $12$ $Pre-dose$ $0$ $1$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ | to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I | to       -1       Image: relation of the stress of | to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I | to       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-<br>dose       0       1       2       3       5       8       12       Pre-<br>dose       0       1       2       3       5       8         Image: Constraint of the constraint | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1 <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       11       2       3       5       8       12       2       2       3       5       8       12       2       2       11       11       11       11       11       11       11       11       11       11       11       11       11</td><td>to       1       <math>\cdot</math> <math>\cdot</math>&lt;</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>to       1                                                                                                              </td><td>21       1       1       1       2       3       4       7         2       1       1       2       3       5       8       12       Pre-dose       0       1       2       3       4       7         1       Pre-dose       0       1       2       3       5       8       12       Pre-dose       0       1       2         1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th< td=""><td>21                                               </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>21       1      </td><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>21       1       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -</td><td>21       1                                </td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>21       1       1       1       1       1       1       1       2       3       4       7       3       4       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></th<></td></t<> | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       11       2       3       5       8       12       2       2       3       5       8       12       2       2       11       11       11       11       11       11       11       11       11       11       11       11       11 | to       1 $\cdot$ < | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | to       1 | 21       1       1       1       2       3       4       7         2       1       1       2       3       5       8       12       Pre-dose       0       1       2       3       4       7         1       Pre-dose       0       1       2       3       5       8       12       Pre-dose       0       1       2         1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 <th< td=""><td>21                                               </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>210       1      </td><td>21       1      </td><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>21       1       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -</td><td>21       1                                </td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>21       1       1       1       1       1       1       1       2       3       4       7       3       4       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></th<> | 21 | 210       1 | 210       1 | 210       1  | 210       1 | 21       1 | 21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V | 21       1       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       - | 21       1 | 21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 <th1< th=""> <th1< th=""></th1<></th1<> | 211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111 | 21       1       1       1       1       1       1       1       2       3       4       7       3       4       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       6       1       2       3       5       8       2       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7       7 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 |

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined at the end of Table 5

Page 2 of 4



#### CYCLE CYCLE 1 ONLY -21 11 15 22 DAY(S) 1 2 3 4 7 8 9 10 -1 to -2 24h 48h after after D9 D9 24h 48h after after HOUR(S) (relative Pre-dose 12 Pre-dose 0 Predose 0 Pre-8 12 0 5 2 5 8 1 2 3 5 0 1 2 3 5 8 12 1 2 3 8 1 3 12 to time of dosing) dose D2 D2 dose dose dose dose **BIOMARKER and DISEASE ASSESSMENTS** MM SUBJECTS ONLY SPEP/UPEP/ Х Immunofixation (15) )TOV( Х SFLC (16) Beta-2 Х microglobulin Quantitative Ig (17) Х Bone marrow Х biopsy Х Plasmacytoma (19) Skeletal survey (20) Х Page 3 of 4

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined at the end of Table 5



CYCLE																				CYCL	E 1 C	DNLY																	
DAY(S)	- 21 to -2	-1		•		1	I						2				3		4	7				8							9					10	11	15	
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	Pre- lose	0	1	2	3	5	8	12 aft D	lh 48 er af 2 D se do	ter 02	Pro do:	e- 0 s€	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	24h after D9 dose	D9		
NHL SUBJECTS	0	۱L'	<u>Y</u>																																				
Lymph Node Biopsy	х																																						
Whole blood plasma (Dose expansion only) (21)	x																																						
Bone marrow biopsy (22)	х																																						
PET-CT and CECT Imaging (23)	х																																						
MRI Brain (24)	х																																						
L			1																											I					F	Page	4 of	4	L

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined at the end of Table 5

Page 67 of 130

Approved

Foot	tnotes for Table 4 and Table 5
1	Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
2	• Three baseline ECGs (pre-dose on day 1) will be collected approximately ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run
	consecutively (ie, < 30 seconds apart); Total of 9 ECGs]
-	Triplicate ECGs run consecutively (ie, < 30 seconds apart), at time points designated in the schedule of assessments
3	See Section 6.5.7 for more details regarding hospitalization for TLS prophylaxis
	Hospitalization for the purpose of TLS prophylaxis will not be captured as an SAE.
4	See Section 6.5.7 for more details regarding TLS prophylaxis.
5	See Section 6.2.1.1 for details regarding dosage, administration, and schedule.
	See Section 6.2.1.1.1 and Table 5 for details regarding dosage, administration, and schedule once lead-in dosing is implemented.
6	For Dose Expansion subjects only:
	<ul> <li>Collected during LTFU period</li> </ul>
7	<ul> <li>For PK collections on Cycle 1, PK samples should be collected within +/- 15 min of the designated time points.</li> </ul>
	• PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as
	close as possible and record the actual collection time in the eCRF.
	Note: It is important to document the exact date and time of IP administration and PK collection.
8	Refer to Section 7.2.15 for list CBC lab tests required.
	Note: Subjects with a Grade 4 neutropenia should have their counts repeated every 24-48 hours until return to baseline and the use of G-CSF should
_	be considered.
9	Refer to Section 7.2.15 for list Chemistry panel lab tests required.
	See Section 6.5.7 for chemistry lab tests required for TLS prophylaxis and management
	Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints for females of childbearing potential.
11	Please collect urine for UA, which is done per local lab.
	Any remaining urine will be sent to the central lab for analysis. Please refer to lab manual for preparation and transport procedures.
	On cycle 1, day 1, collect urine sample at least 5 hours post-dose of AMG 397.
	After cycle 1, urine sample may be collected at the following designated timepoints.
12	A bone marrow aspirate will be collected from all subjects during screening for IHC testing, to quantify percent tumor involvement, for fluorescent in situ
	hybridization (FISH) and other biomarker assays.
13	• Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on day 1, and 24 hours after day 1 during
	week 1 as indicated in Table 4.
	• Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follows: In the second week of Cycle 1, samples will be
	collected pre-dose on day 8, 3 and 5 hours post dose on day 8, and 24 hours after day 8.
14	Biomarker Cytochex whole blood samples will be collected pre-dose on days 1, 2, 3, 4, and 8 as indicated in Table 4.
	• Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follow: pre-dose on days 9, 10, and 15.



For	MM subjects only [15-20]:
15	• Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening.
	Thereafter, SPEP is to be done at each time point for all patients as indicated in the schedule of assessment.
	<ul> <li>UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP is negative, spot urine is required at each time point.</li> </ul>
	<ul> <li>If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.</li> <li>See lab manual for collection and shipment details.</li> </ul>
46	See lab manual for collection and shipment details.     Serum free light chain (SFLC) assay and ratio will be performed at each marked time point.
<u>16</u> 17	
	Quantitative Immunoglobulin (Total IgG, IgA, IgM) obtained at screening and will be repeated only if clinically indicated (ie; frequent infection despite multiple myeloma disease control).
18	Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.
19	Plamacytoma survey
	• For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable.
	• Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically
	indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care
	method) must be employed for each measurement.
20	Skeletal survey to be repeated Q8W if clinically indicated ie; new symptoms (bone pain) arises, consider obtaining MRI for subjects with bone pain but skeleta
	survey is normal.
	L ( subjects only [21-24]:
21	For dose expansion subjects only:
	• Whole blood plasma may be obtained pre-dose on day 1 of Cycle 2, and every 8 weeks thereafter, and EOT. Samples must be collected, processed, and
	frozen within 4 hours of phlebotomy and per the laboratory manual.
	Additional whole blood plasma samples are obtained at time of relapse.
22	Bone marrow evaluation (core biopsy with or without aspirate) may be performed if there has been previous histologic evidence of bone marrow involvement. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.
23	PET-CT and CECT Imaging with time points at screening, Cycle 2, every 8 weeks thereafter, and EOT. If not acquired on the same day, every effort should be made to complete PET-CT and CECT within 3 days of each other.
24	For Both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI/CT of the brain performed within 21 days prior to enrollment.
	All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable. Subsequently, MRI brain can be
	performed at any time if clinically indicated per standard of care.
25	For AML Subjects only [25]:
	Bone marrow samples must be obtained at pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and EOT.
	Additional bone marrow sampling may occur at other time points at the PI's discretion as clinically indicated throughout course of treatment
26	For Dose Expansion subjects only:
-	Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not
	withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.



#### 7.2 Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study specific procedures are performed. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

For more information regarding subject enrollment, refer to Section 5.

#### 7.2.1 Medical History

The Investigator or designee will collect a complete medical and surgical history that started at least 2 years prior to enrollment through the through first dose of AMG 397. Medical history will include information on the subject's concurrent medical health conditions, relevant past medical conditions, and surgical history. Record all findings on the medical history eCRF.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

#### 7.2.2 Prior Therapy

The Investigator or designee will collect relevant prior therapy, which includes previous chemotherapy, radiotherapy, investigational drug, and any anticancer therapies (eg, stem cell transplant). Prior therapies that were being taken prior to enrollment through the first dose of IP should be collected.

Record all findings on the prior therapy eCRF.

#### 7.2.3 Physical Examinations

A complete physical examination will be performed by the investigator or designee according to local practices at screening and time points specified in the Schedule of Assessments (Section 7.1).

#### 7.2.4 Height Measurements

Height (cm) will be measured without shoes at screening.

#### 7.2.5 Weight Measurements

Weight (kg) without shoes will be obtained at screening and time points specified in the Schedule of Assessments (see Section 7.1)



#### 7.2.6 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure (BP), respiratory rate, heart rate and temperature. Subject must be in rested and calm state for at least 5 minutes before BP assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs/temperature eCRF. Vital signs will be recorded by the investigator or qualified site personnel at screening and time points specified in the Schedule of Assessments (see Section 7.1).

Abnormal measurements may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF page. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn.

#### 7.2.7 Electrocardiogram Performed in Triplicate

The subject should rest for at least 5 minutes before ECG assessment is conducted. Electrocardiograms should be performed in a standardized method, in triplicate (at designated time points), and run consecutively, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Electrocardiograms will be performed as follows:

- Three baseline ECGs (pre-dose on day 1) will be collected approximately
   ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run
   consecutively (ie, < 30 seconds apart); Total of 9 ECGs]</li>
- Triplicate ECGs run consecutively (ie, < 30 seconds apart), at time points designated in the schedule of assessments

The principal investigator or qualified site personnel will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central vendor for reconciliation and storage per Amgen instructions. Once reviewed, the original ECG tracing will be retained with the subject's source documents. At the request of Amgen, a copy of the original ECG will be made available to Amgen.

Standard ECG machines should be used for all study-related ECG requirements, this will be provided to the site as ECG data will need to be transmitted to the selected vendor.



#### 7.2.8 Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will be performed at time points specified in the Schedule of Assessments (see Section 7.1). Additional ECHO/MUGA, cardiac imaging and cardiac assessments are to be conducted if any clinical signs or symptoms of cardiomyopathy or other cardiac compromise are noted.

#### 7.2.9 Dosing Diary Review

A dosing diary will be provided for subjects to record the date, time, and number of tablets consumed each dose. The dosing diary is to be brought to each study visit and reviewed by study staff (see Section 7.1).

The dates of any missed doses or instances of emesis associated with tablet administration will asked to be recorded in the subject drug diary.

#### 7.2.10 Assessments in MM Subjects

# 7.2.10.1 Serum Protein Electrophoresis (SPEP) and Urine Protein Electrophoresis (UPEP)

Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening. Thereafter, SPEP is to be done at each time point for all subjects as indicated in the schedule of assessments.

UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine and for confirmation of VGPR or CR as per IMWG-URC. If screening UPEP is negative, spot urine is required at each time point. If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.

#### 7.2.10.2 Serum Free Light Chain

Serum free light chain (SFLC) assay and ratio will be performed at each time point as specified in the schedule of assessments.

#### 7.2.10.3 Quantitative Immunoglobulin

Quantitative Immunoglobulin (Ig) will be performed at screening and at each time point as specified in the schedule of assessments. Quantitative Immunoglobulin will be repeated only if clinically indicated, ie, frequent infection despite Multiple Myeloma disease control or deemed clinically indicated by the investigator.



#### 7.2.10.4 Beta-2 Microglobulin

Beta-2 microglobulin will be performed at baseline as part of risk stratification and at each time point as specified in the schedule of assessments.

#### Plasmacytoma Survey

Plasmacytoma survey will be performed at the time points as specified in the schedule of assessments (Section 7.1). For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable.

Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.

## 7.2.10.5 Skeletal Survey

Skeletal Survey (conventional radiography, whole body low-dose CT, PET-CT or MRI) will be performed at the time points as specified in the schedule of assessments (Section 7.1). It can also be done if clinically indicated, ie, new symptoms (bone pain) arise. MRI should be performed in subjects with bone pain but skeletal survey is normal.

## 7.2.10.6 Bone marrow

Bone marrow sample and biopsy will be collected during the screening to quantify percent myeloma involvement and for fluorescent in situ hybridization (FISH).

Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.

## 7.2.11 Assessments in NHL Subjects

## 7.2.11.1 Imaging and Disease assessments

Clinical tumor assessments will be performed as indicated in the schedule of assessments and per institutional guidelines. The Lugano Classification will be used to assess treatment response as described in Appendix I.

PET-CT and CECT scans required in this protocol will be performed according to the Imaging Manual provided by the central vendor. However, depending on scanner types and availability, as well as local regulations, institutional guidelines may be followed upon consultation with, and approval by, the central vendor. Combined PET-CT whole body scans will be acquired from base of skull to mid-thigh, with the CT portion of the



scan used only for attenuation correction. CECT anatomical coverage includes the chest, abdomen, and pelvis (and neck, if not visualized with chest), and the acquisition of separate CECT scans is strongly recommended for staging evaluation. Refer to the Imaging Manual for complete details about PET-CT and CECT scanning procedures and instructions.

PET-CT images should be converted to standardized uptake values (SUV) maps to support comparison across timepoints and to standardize viewing conditions.

If PET-CT and CECT are acquired on the same day, it is strongly recommended that PET-CT is performed prior to CECT. If acquired separately, every attempt should be made to complete PET-CT and CECT within 3 days of each other.

Refer to the Imaging Manual for additional details. Findings will be recorded per eCRF guidelines.

## 7.2.11.2 MRI Brain

For both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI or CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.

## 7.2.11.3 Lymph Node and Bone Marrow Assessments

Lymph node and bone marrow biopsy are to be collected as per schedule of assessments.

Bone marrow evaluation (core biopsy with or without aspirate) should be performed if there has been previous histologic evidence of bone marrow involvement plus a negative or ambiguous PET-CT, or if bone marrow involvement is suspected with an ambiguous or negative PET-CT. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.

Refer to the Laboratory Manual for additional information for these procedures.

## 7.2.11.4 Whole Blood Plasma

For dose expansion subjects (DLBCL subjects) only:

- Whole blood plasma may be obtained at pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and EOT. Samples must be collected, processed, and frozen within 4 hours of phlebotomy. See laboratory manual for more details
- Additional whole blood plasma samples are obtained at time of relapse.



#### 7.2.12 Assessments in AML Subjects

Bone marrow aspirate will be performed for the following:

- Hematocytology and cytochemistry to establish WHO subtype of AML local site laboratory according to local procedures using slides of bone marrow and peripheral blood
- Immunological phenotyping to verify myeloid leukemia. Additional immunological phenotyping and/or MRD will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation
- Cytogenetics (gene expressions, gene mutations, cell culture and banding analysis) a local laboratory may perform cytogenetics to determine eligibility at screening. Previous bone marrow aspirate or biopsy performed within 6 months of day 1 may be used to determine eligibility for subjects. A bone marrow biopsy or aspirate will still be required during screening for all subjects.
- Additional cytogenetics will be performed/done at the investigator's discretion, for relapsed and/or for response confirmation.
- Bone marrow biopsy for histopathology in case of dry tap

Additional bone marrow sampling may occur at other time points at the investigator's discretion as clinically indicated. Unscheduled bone marrow aspirate results will be captured in the respective eCRFs.

#### 7.2.12.1 Disease Response in AML Subjects

Disease response assessments will be based upon review of bone marrow aspirates, and peripheral blood count. Refer to the 2017 ELN criteria in Appendix J for additional details. Complete response/complete recovery with incomplete count recovery (CRi) must be established from a bone marrow samples supplemented with neutrophil, platelet, and peripheral blast counts.

In case of transplantation, a CR or CRi must be confirmed within 4 weeks prior to transplantation.

## 7.2.13 Pharmacokinetic Blood Sampling

For pharmacokinetic assessment blood samples for quantitative determination of AMG 397, will be collected at time points specified in the Schedule of Assessments (Section 7.1). Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

#### 7.2.14 Blood Samples

Approximate blood volumes expected to be collected during study participation (screening, treatment period of 6 months, and EOT/SFU visits) are presented in the tables below.



		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry Pregnancy test (childbearing females only)	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Quantitative Immunoglobulin	10	2	20	2	20
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Beta-2 microglobulin, SPEP and SFLC	10	7	70	7	70
Total approximate blood volu		<u>520</u>		<u>762.5</u>	

## Table 6. Approximate Blood Volumes Collected for MM Subjects Only

## Table 7. Approximate Blood Volumes Collected for NHL Subjects Only

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry <ul> <li>Pregnancy test <ul> <li>(childbearing</li> <li>females only)</li> </ul> </li> </ul>	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume for dose		escalation	488.5		<u>672.5</u>
Whole blood plasma (Dose expansion subjects only)	5	5	25	5	25
Total approximate blood volu	expansion	<u>513.5</u>		<u>697.5</u>	

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximate Number of Collection	Approximate Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry <ul> <li>Pregnancy test <ul> <li>(childbearing</li> <li>females only)</li> </ul> </li> </ul>	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
<u>Total approximate blood</u> <u>volume</u>			<u>488.5</u>		<u>672.5</u>

#### Table 8. Approximate Blood Volumes Collected for AML Subjects Only

## 7.2.15 Clinical Laboratory Assessments

The following laboratory analytes in Table 9 will be assessed as specified in the

Schedule of Assessments (Section 7.1) collected by standard laboratory procedures.

<u>Chemistry</u>	Hematology	<u>Urinalysis</u>	<u>Coagulation</u>	For MM Subjects
Albumin	ANC	Specific gravity	PT or INR	<u>only:</u>
ALP	Hematocrit	рН	Activated Partial	SPEP
ALT	Hemoglobin	Blood	Thromboplastin Time	UPEP
AST	MCH	Protein	(APTT)	SFLC
Bicarbonate	MCHC	Ketones	Other Labo	Quantitative
BUN or Urea	MCV	Bilirubin	Other Labs	Immunoglobulin
Calcium	Platelets	Glucose	Pregnancy	Beta-2
Chloride	RBCs	Leucocytes	Hep B surface antigen	microglobulin
Creatinine	WBCs	esterase (WBC)	Hep B antibody	
Direct bilirubin	Differential:	Microscopic exam	Hep C antibody HCV PCR (if	For NHL subjects
GGT	<ul> <li>Neutrophils</li> </ul>	(only needed for	•	<u>only:</u>
Glucose	<ul> <li>Lymphocytes</li> </ul>	positive dipstick	applicable) HBV PCR (if	Whole blood
LDH	<ul> <li>Monocytes</li> </ul>	and should include	applicable)	plasma
Magnesium	<ul> <li>Eosinophils</li> </ul>	the following):	applicable)	Lymph node
Phosphorus	<ul> <li>Basophils</li> </ul>	Epithelial,	PK (including urine for	biopsy
Potassium		Bacteria, Casts,	analysis)	
Sodium		Crystal, RBCs,	Biomarker analytes	
Total bilirubin		WBCs	(See Section 7.3)	
Total protein			Bone marrow aspirate	
Total bile acid			as applicable	
Uric acid			Bone marrow biopsy	
Haptoglobin			as applicable	
			as applicable	

 Table 9. Clinical Laboratory Assessments



#### 7.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to AMG 397 or protocol required therapies. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 397 to investigate and further understand the importance of the intrinsic apoptotic pathway family members in heme malignancies.

Biomarker development may be pursued by use of advanced biochemical analyses in blood, bone marrow, or tumor tissue samples, encompassing proteomic methods, genomic sequencing, or ribonucleic acid transcript profiling. Biomarkers such as pro-survival family members will be explored (eg, MCL1, BCL2, and BCL2L1 expression), as well as the larger family of apoptosis pathway proteins, chromosomal aberrations and translocations, somatic mutations, molecularly defined disease subgroups, and analysis of minimal residual disease.

**Please NOTE**: Sample collection, processing, storage, shipping instructions and schedules are provided in a separate laboratory manual.

## 7.3.1 Blood Samples

Whole blood samples are to be collected for biomarker measurement at several time points as listed in the schedule of assessments. The first set of samples will be collected for Flow cytometric analysis to measure the increase in BAX and Caspase 3 activity in circulating monocytes (MM, NHL) or peripheral blasts (AML) following treatment with AMG 397.

Initially, these blood samples will be collected on Cycle 1 pre-dose on day 1, 3 and 5 hours post-dose on day 1, as well as pre-dose on day 2 according to Table 4. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on Days 1 and 2, 3 and 5 hours post-dose on Day 1, as well as pre-dose on Days 8 and 9, 3 and 5 hours post-dose on Day 8.



In AML subjects, these whole blood samples may also be used to measure pro-survival family members (such as MCL1, BCL2, and BCL2L1 expression) in peripheral leukemic blasts.

A second set of biomarker blood collections will be used to monitor cell counts of immune cell subsets, including T cells, B cells, NK cells, monocytes, and Myeloid Derived Suppressor Cells (MDSCs) following treatment with AMG 397. Initially, these samples will be collected on Cycle 1 pre-dose on days 1, 2, 3, 4, and 8 according to Table 4 above. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on days 1, 2, 3, 4, 8, 9, 10, and 15.

For NHL subjects in Part 2 during dose expansion, additional whole blood samples may be taken to assess clinical responses through depth of minimal residual disease status as indicated in schedule of assessments.

#### 7.3.2 Bone Marrow

During screening, bone marrow aspirates are required for all subjects. A core bone marrow biopsy is required for all multiple myeloma subjects. Samples may be analyzed for protein expression and activity using immunohistochemistry and/or flow cytometry, and RNA transcript expression using platforms including Nanostring, RNA sequencing, and/or droplet digital PCR. Analyses of tumor specific mutations or epigenetic changes may be performed using FISH, array technologies or next generation sequencing. In Part 2, minimal residual disease may be evaluated on additional bone marrow specimens as indicated in the schedule of assessments (Table 4. and/or Table 5) in MM and AML subjects.

## 7.3.3 Tumor Biopsy

For NHL subjects, a tumor biopsy at the primary lymph node site is required at screening. An additional tumor biopsy may be collected at time of relapse per institutional guidelines and PI discretion.

Protein expression of pro-survival family members (such as MCL1, BCL2, and BCL2L1) will be analyzed via immunohistochemical methods. Genomic and RNA transcriptional analyses may be further performed including but not limited to FISH, and determination of MRD by NGS.



#### 7.4 General Study Procedures

Cycle 1 and 2 visits should be done on days specified as possible. All subsequent visits beginning on Cycle 3 will have a +/-1 day window unless otherwise specified.

## 7.4.1 Screening

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Section 7.1).

- Confirmation that the Informed Consent Form has been signed
- Demographic data including sex, age, race, and ethnicity
- Clinical evaluations include physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory Assessments including local and central laboratories, as applicable
- Pregnancy test as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- ECG
- ECHO/MUGA
- For NHL subjects, MRI brain (See Section 7.2.11.2)
- Serious Adverse Event reporting
- Documentation of concomitant and rescue medications

Subjects may be rescreened at the discretion of the investigator after consultation with the Amgen Medical Monitor. Refer to Section 5 for instructions on rescreening and enrolling subjects.

#### 7.4.2 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Section 7.1). Administration of AMG 397 is to be administered as applicable during each visit that it is required.

Treatment visits to include the following:

- Hospitalization (See Section 6.5.7)
- TLS prophylaxis (See Section 6.5.7)
- Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight.
- AMG 397 dosing



- Dosing diary review
- PK (including intensive PK assessments)
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

## 7.4.3 End of Treatment Visit

The end of treatment (EOT) visit will occur after the last dose of AMG 397. The end of treatment (EOT) visit will occur upon the decision to end the treatment, disease progression, intolerable adverse event, documented clinical progression or consent withdrawal.

For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Serious adverse events considered related to the investigational product, by the Investigator, or Amgen will be followed until resolved or considered stable.

EOT visits to include the following:

- Clinical evaluations include: physical exam, ECOG status, and weight.
- Dosing diary review
- PK
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable



- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

## 7.4.4 Safety Follow-Up (SFU) Visit

The SFU visit must be performed approximately 28 (+7) days after the last dose of AMG 397. All efforts should be made to conduct this visit. If it is not possible to conduct the SFU visit, documentation of efforts to complete the visit should be provided in the source documents and noted as not done in the eCRFs.

- Clinical Evaluation
- ECG
- Visit signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- Laboratory assessments including local and central laboratories, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

#### 7.4.5 Long-term Follow-up (Dose expansion subjects only)

Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.

#### 7.5 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be extracted and performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of MM, NHL and/or AML and to identify subjects who may have positive or negative response to AMG 397. No additional samples are collected for this part of the study.

## 7.6 Sample Storage and Destruction

Any blood, bone marrow or tumor sample collected according to the Schedule of Assessments (Section 7.1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the



study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the Multiple Myeloma, NHL, and AML, disease indications, the dose response and/or prediction of response to AMG 397, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the Investigator is to provide the sponsor with the required study and subject number so that any remaining blood, bone marrow, or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

Amgen is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, Amgen owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or



derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

# 8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY 8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Section 7.1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and disease related events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

#### 8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the



local country's regulatory mechanism, based on parameters consistent with Section 12.1.

#### 8.3 Reasons for Removal From Treatment or Study

#### 8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor
- disease progression
- protocol specified criteria

#### 8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

## 9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

#### 9.1 Definition of Safety Events

#### 9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves



an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Record a single event for each increased level of severity on the Event eCRF.

For situations when an adverse event or serious adverse event is due to Multiple Myeloma or Non-Hodgkin's Lymphoma report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma).

**Note:** The term "disease progression" should not be used to describe the adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

#### 9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.



## 9.2 Safety Event Reporting Procedures

## 9.2.1 Adverse Events

## 9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of Safety Follow-Up(SFU)/end of study (EOS) visit are reported using the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to investigational product, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each increase in level of severity on the Adverse Event Summary eCRF.

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment



or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

## 9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of investigational product are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event eCRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization, resolution or patient death.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records.



Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local regulatory requirements and procedures.

## 9.2.1.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

## 9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 397 report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 3 months after the last dose of AMG 397.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 3 months after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

#### 10. STATISTICAL CONSIDERATIONS

#### 10.1 Study Endpoints

#### Primary Endpoints:

• Incidence of dose limiting toxicities (DLTs), treatment-emergent adverse events, treatment-related adverse events, and clinically-significant changes in vital signs, physical examinations, electrocardiogram (ECGs) and clinical laboratory tests

#### Secondary Endpoints:

- Efficacy parameters:
  - ORR using response criteria per the following:
    - International Myeloma Working Group (IMWG) for MM subjects
    - Lugano Classification for NHL subjects
    - Revised International Working Group (IWG) for AML subjects



- Duration of response
- Progression Free Survival (PFS) and Overall Survival (OS)
- AMG 397 PK parameters including, but not limited to, maximum observed concentration (C<sub>max</sub>), time of maximum observed concentration (T<sub>max</sub>), area under the concentration-time curve (AUC), clearance (CL) and half-life (t<sup>1/2</sup>)

## **Exploratory Endpoints:**

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

## 10.1.1 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 397. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.1.1). The PK Analysis Set will contain all subjects who have received at least 1 dose of AMG 397 and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

## 10.2 Covariates and Subgroups

The relationship between baseline covariates and safety/efficacy endpoints will be explored. Safety and efficacy endpoints will be summarized separately for each tumor type. Details regarding covariates and subgroups and respective analyses are described in the Statistical Analysis Plan.

## 10.3 Sample Size Considerations

Up to 90 subjects will be enrolled in the study. Up to 60 subjects will be enrolled during dose escalation (up to 30 in both Group 1A and 1B). Up to 30 subjects will be enrolled into the dose expansion part (up to 10 in each Group 2A, 2B & 2C).

The sample sizes are based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the MTD. During



dose-escalation and with 3 subjects in a cohort, there is a 27 to 70% probability of observing at least one DLT if the true DLT rate is 10 to 33%. With 10 subjects respectively in in dose expansion group, there is a 40% to 65% probability of observing at least 1 adverse event if the true event rate is 5% to 10%. Exact 80% binomial CI will be provided for ORR. With the 10 subjects in each dose expansion group and a 20% ORR, the 80% CI would be 5% to 45%.

## 10.4 Adaptive Design

A 2-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose escalation. The MTD target Toxicity Probability Interval (TPI) for DLT is (0.20, 0.33] and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The overdose control limit is defined as less than a 0.40 probability of an excessive or unacceptable TPI. Based on accumulating safety data, the DLRT may implement an overdose control limit of less than a 0.25 probability of an excessive or unacceptable TPI. The probability of a DLT at dose level d<sub>i</sub> is assumed to follow a Bernoulli distribution with probability p<sub>i</sub> where the logit of p<sub>i</sub> increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

 $\log [p_i / (1-p_i)] = logit(p_i) = log[a] + exp( log[b]) log (d_i / d_{ref})$ 

where a and b are random variables and  $d_{ref}$  is 1 of the planned dose selected as the reference dose.

A bi-variate normal prior distribution (Neuenschwander et al, 2008) is used for theta = (log a, log b) where the probability that the true DLT rate is  $\leq$  0.40 at the lowest planned dose of 80 mg is 0.90 and the probability the true DLT rate is  $\leq$  0.05 at the reference dose of 640 mg is 0.05. These values are selected such that p<sub>i</sub> is 0.05 for the starting dose and 0.25 for the reference dose. Model sensitivity to the prior will also be investigated and in particular the BLRM will be examined using a prior having a lower reference dose (eg, 320 mg). Operating characteristics for this BLRM design are described in Appendix D.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher adverse event rate to assess if the threshold for early trial termination has been reached. The stopping rules use a Bayesian approach proposed by Thall, et al (1995) to terminate



the study if the posterior probability that the grade 4 or higher adverse event rate is greater than 20% is > 90%. The stopping boundaries assuming a prior distribution of Beta (0.40, 1.60) are presented in Table 10 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 2. Subjects including in a batch may come from different tumor types. The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 11 provide the probability of stopping the study early for given hypothetical true rate of grade 4 or higher adverse events, whereas the stopping criteria in Table 10 are based on situations where the empirical evidence would result in a posterior probability of  $\geq$  90% that the true grade 4 or higher adverse event rate is  $\geq$  20%.

Table 10. Stopping Boundary for Dose Expansion With Posterior Probability of90% and Grade 4 or Higher Adverse Event Limit of 20%

Number of subjects	Stop study if observing these many grade 4 or higher advers events	
10	≥5	
20	≥7	
30	Study Complete	

#### Table 11. Operating Characteristics With Batch Size of 10 Subjects

True grade 4 or higher adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	0.4%	29.9
0.15	2.7%	29.6
0.20	9.7%	28.7
0.25	22.9%	26.9
0.30	40.8%	24.4

## 10.5 Planned Analyses

## 10.5.1 Interim Analyses

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In dose level review team meetings (DLRMs), Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a one-parameter Continual Reassessment Method (CRM) model may be used to estimate



the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

An interim analysis for efficacy parameters will be conducted after dose escalation is completed.

## 10.5.2 Dose Level Review Team (DLRT)

After reviewing all available safety data and reviewing the dose recommendation from the BLRM, the DLRT will make all dose level and dosing schedule decisions. Details regarding the DLRT and the process for making dosing decisions are described in Section 6.2.1.2.

## 10.5.3 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or withdraws from the study.

## 10.5.4 Final Analysis

The final analysis will occur after all subjects have ended the study.

#### 10.6 Planned Methods of Analysis

## 10.6.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic and biomarker data by tumor type, dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

## 10.6.2 Primary Endpoints

## Safety Endpoints:

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 397.

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels.

## Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting



adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of adverse events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

#### **Clinical Laboratory Tests**

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

#### Vital Signs

Vital signs data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

#### Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study ECG data will be listed, and select parameters of interest may be plotted.

## 10.6.3 Secondary Endpoints

## 10.6.3.1 Efficacy Endpoint Analyses

The analyses on PFS and OS will be done only using data from dose expansion subjects; other efficacy endpoints will be analyzed using data from both dose escalation and dose expansion.

The number and percentage of subjects by overall response and overall response category will be calculated and tabulated. Using the Kaplan Meier estimate, the PFS at 6 and 12 months and the OS at 6 and 12 months with corresponding 90% CI will be tabulated. Listings will be produced for all subjects indicating the OS, PFS, time to



response and duration of response. Kaplan Meier curve will be presented for OS, PFS, time to response and duration of response with estimates for rates and 80% CI at selected weeks.

## 10.6.3.2 Pharmacokinetics Data Analysis

For AMG 397, PK parameters including including  $C_{max}$ ,  $T_{max}$ , AUC, CL and half-life will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 397 exposure and either pharmacodynamic effects and/or clinical outcome may also be performed.

## 10.6.4 Exploratory Endpoints

The following statistical analyses will be considered exploratory and will be performed only when deemed appropriate.

Summary statistics over time will be provided and graphical presentations may be used to describe the following.

- AMG 397 exposure/efficacy and exposure/safety relationships
- AMG 397 metabolites in plasma and urine
- Increased expression of BAX and Caspase 3 in monocytes or blast cells and/or decrease in circulating monocyte counts
- Patient responses according to biomarkers of tumor cells including but not limited to protein levels of pro-survival family members, FISH/cytogenetic analysis, gene expression profiling, flow cytometric phenotyping and DNA sequencing
- Immune cell subset frequencies, absolute counts and MFIs in peripheral blood
- MRD status

The relationship between AMG 397 exposure and PD effects and related biomarkers in blood, or tumor specimens and/or AMG 397 exposure and clinical outcomes (eg, tumor response) will be also explored if deemed appropriate. Based on the review of the safety and efficacy data, analyses to describe the relationship between AMG 397 exposure and safety/efficacy endpoints may also be performed.

## 11. **REGULATORY OBLIGATIONS**

## 11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator.



The written informed consent form is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. *Refer to ICH GCP guideline, Section 4.8.9.* 

## 11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent



document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

## 11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

## 11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects



#### 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

#### 12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

## 12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.



Elements to include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

#### 12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.



Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF Standard Instructions and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

## 12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Section 7.1), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

## 12.5 Language

eCRFs must be completed in English. TRADENAMES<sup>®</sup> (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.



#### 12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.



#### 12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.



#### 13. **REFERENCES**

AMG 397 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405.

Ardeshna KM, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. Br J Haematol. 2005;130(3):363-372.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Statistics in medicine. 1998: 17(10):1103-1120

Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. *Nature*. 2010:463:899-905.

Bose P and Grant S. Mcl-1 as a therapeutic target in acute myelogenous leukemia (AML). *Leukemia Research Reports*;2013;2(1):12-14.

Boyle MC, Crabbs TA, Wyde ME, et al. Intestinal lymphangiectasis and lipidosis in rats following subchronic exposure to indole-3-carbinol via oral gavage. *Toxicol Pathol.* 2012;40:561-562.

Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 2005;23:1969-78.

Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol 2011a;29:487-94.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

Crump M, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496.

Czabotar PE, Lessene G, Strasser A and Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nat Rev Mol Cell Biol.* 2014:15;49-63.

DeVita VT Jr, et al. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet. 1975;1(7901):248-50.

Dimopoulos MA, Richardson PG, Moreau P, Anderson KC. Current treatment landscape for relapsed and/or refractory multiple myeloma. *Nat Rev Clin Oncol.* 2015;12:42-54.

Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD; European LeukemiaNet. Blood. 2010 Jan 21;115(3):453-74.



Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: 2017 ELN recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2017;129(4):424-447.

Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467–73. Erratum in: *Leukemia*. 2006;20(12):2220. *Leukemia*. 2007;21(5):1134.

Durie BG, International Myeloma Foundation. Multiple Myeloma Cancer of the Bone Marrow. Concise Review of the disease and treatment Options. 2011/2012.

Elstrom RL, et al. Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. Clin Lymphoma Myeloma Leuk. 2010;10(3):192-196.

Estey E. Acute myeloid leukemia: 2016 Update on risk-stratification and management. Am J Hematol. 2016 Aug;91(8):824-46.

Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia* 2000;14:476-9.

Estey E, Kornblau S, Pierce S, Kantarjian H, Beran M, Keating M. A stratification system for evaluating and selecting therapies in patients with relapsed or primary refractory acute myelogenous leukemia. *Blood* 1996;88:756

Fisher SG and Fisher RI. The Epidemiology of Non-Hodgkin's Lymphoma. Oncogene. 2004;23(38):6524-534.

Glaser SP, Lee EF, Trounson E, Bouillet P, Wei A, Fairlie WD, et al. "Anti-apoptotic Mcl 1 is essential for the development and sustained growth of acute myeloid leukemia." Genes & Development 2012; 26(2): 120-125.

Haematological Malignancy Research Network.https://www.hmrn.org/statistics/incidence

Hanahan D and Weinberg RA. "Hallmarks of Cancer: The Next Generation." *Cell* 2011; 144(5): 646-674.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

Kasper S, Breitenbuecher F, Heidel F, Hoffarth S, Markova B, Schuler M and Fischer T "Targeting MCL-1 sensitizes FLT3-ITD-positive leukemias to cytotoxic therapies" *Blood Cancer J* 2012; 2, e60.

Kaufmann SH, Karp JE, et al. "Elevated Expression of the Apoptotic Regulator Mcl-1 at the Time of Leukemic Relapse". *Blood* 1998; 91(3)991-1000.

Kewalramani T, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103(10):3684-3688.

Kozopas KM, Yang T, Buchan HL, Zhou P, and Craig RW. MCL1, a gene expressed in programmed myeloid cell differentiation, has sequence similarity to BCL2. *Proc Natl Acad Sci U S A*. 1993:90;3516-3520.

Martin A, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica. 2008;93(12):1829-1836.



Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine. 2008;27(13):2420-2439

Palumbo A, Anderson K. Multiple Myeloma. N Engl J Med 2011;364:1046-60

Peperzak V, Vikström I, Walker J, Glaser SP, LePage M, Coquery CM, et al. "MCL1 is essential for the survival of plasma cells." Nat Immunol 2013; 14(3): 290-297.

Philip T, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med. 1987;316(24):1493-1498.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-4695

Ravandi F. Relapsed acute myeloid leukemia: why is there no standard of care? Best practice & research 2013;26:253-9.

Ravandi F, Cortes J, Faderl S, et al. Characteristics and outcome of patients with acute myeloid leukemia refractory to 1 cycle of high-dose cytarabine-based induction chemotherapy. *Blood* 2010;116:5818-23; quiz 6153.

Robinson SP, et al. Autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma: efficacy in the rituximab era and comparison to first allogeneic transplants. A report from the EBMT Lymphoma Working Party. Bone Marrow Transplant. 2016;51(3):365-371.

Sehn LH and Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.

Smith D, Yong K. Multiple myeloma. BMJ. 2013 Jun 26;346:f3863. doi: 10.1136/bmj.f3863. Review.

Smith D, Yong K. Multiple Myeloma. BMJ 2013;346:f3863 doi: 10.1136/bmj.f3863. Society AC. Cancer Facts and Figures, 2017. Atlanta, George, USA: American Cancer Society; 2017.

Strasser A, Cory S, and Adams JM. Deciphering the rules of programmed cell death to improve therapy of cancer and other diseases. *Embo j.* 2011:30;3667-3683.

Swerdlow SH, et al. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. Blood. 2016

Thall P, Simon R, Estey E. "Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes", Statistics in Medicine, vol 14, 357-379 (1995).

Thomas RL, Roberts DJ, Kubli DA et al. Loss of MCL-1 leads to impaired autophagy and rapid development of heart failure. *Genes Devel.* 2013;27:1365-1377.

Tilly H, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):116-125.

van Delft MF, Wei AH, Mason KD, et al. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. *Cancer Cell.* 2006;10:389-399.

Wang X, Bathina M, Lynch J, et al. Deletion of MCL-1 causes lethal cardiac failure and mitochondrial dysfunction. *Genes Devel.* 2013;27:1351-1364.

Wertz IE, Kusam S, Lam C, et al. Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. *Nature*. 2011:471:110-114.



Witzig TE, et al. Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group. Leuk Lymphoma. 2008;49(6):1074-1080.

Xiang Z, Luo H, Payton J E, Cain J, Ley T J, Opferman J T, Tomasson M H. Mcl1 haploinsufficiency protects mice from Myc-induced acute myeloid leukemia. *J Clin Investigation*;2010;120(6):2109-2118.

Youle, R. J. and A. Strasser. "The BCL-2 protein family: opposing activities that mediate cell death." *Nat Rev Mol Cell Biol* 2008; 9(1): 47-59.

Zelenetz AD, et al. Non-Hodgkin's Lymphomas, Version I.2016', National Comprehensive Cancer Network Guidelines.

Ziepert M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(14):2373-2380.

14. **APPENDICES** 



# Appendix A. Additional Safety Assessment Information

# Adverse Event Grading Scale

The CTCAE Version 4.03 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm.

# Drug-induced Liver Injury Reporting & Additional Assessments

# Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.7 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1

# Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.7.1 and Section 6.7.2 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis



- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - o Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - o Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- CPK, haptoglobin, LDH, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.



# Appendix B. eSerious Event Contingency Form

	AMGE		Elec	ctronic	Se	rio	us Ad	vers	e E	ven	t C	o	ntin	ige	ency	R	ep	ort Fo	rm
S	tudy # 201 AMG 39		For Restricted Use																
1	AMG J3	51																	
Rea	ason for rep	orting this ev	ent	via fax															
The	e Clinical Tr	ial Database (	eg. I	Rave):															
	ls not availat	ole due to interr	net d	outage at n	ny si	te													
	ls not yet ava	ailable for this s	tudy	/															
		sed for this stu	-			Ē	X #												
_			-,			_	•.x # :: +888 {	044.06	<u> </u>										
1.5	SITE INFORM					03	. +000 (	514 00	<u>53</u> •										
	Site Number			Investig	ator										Country				
		Reporter				Phone	Number						Fax	Numb	er (				
						(	)						(		)				
2. 5	SUBJECT INF			lan at a set					0						lf -	See. 1		uide End of f	Shudh :
	Subject II	D Number	'	Age at event on	set				Sex	]F 🗆	м	Ra	ece		lf ap date	лсаб	е, рю	wide End of S	ымау
											IVI								
If th	is is a follow-up	to an event report	ed in 1	the EDC sys	stem (	(eg, R	ave), prov	ide the	advers	e even	t tern	n:			-				_
		/ Month	Yea	9r															
		/ERSE EVENT Investigator becar		une of this is	form	ation:	Dav	Month	Va	ar									
		t diagnosis or syndro			norma	ation.	Day	Check		fseriou	<u></u>			Rələti	onship			Outcome	Check only
If diag	gnosis is unknowr	n, enter signe / sympt	emo					only if event	i sn	enter		there			possibility en cause		eEven		If event is related to
and p		when known, in a fol report	IOW-	Date Starte	ed	Date	e Ended	occurred before	serious?	Serious Criteria		oran		device	used to a		ster the	110112-2017-20	study procedure
		lf event is fatal, enter f "death" is not accepta						first dose	event s	code (see				18	D?			-Fatal -Unknown	eg, biops
causi		r death is not accepta an outcome.	H	Day Month	Vore	Day M	onth Year	ofIP	s eve	codes		Ydevio	কাৰ্বম	levice>	<1Pitievic	৯ ব	Pidevice	<i>b</i>	
				Day Monin	Tear L	ay M	onin Tear		_	below)		Yee			No-Ye				
									□ Yes □ No										
									□Yes		$\square$	$\square$				$\top$			
					_				□No □No		+	$\vdash$	-			+	_		
									□Yes □No										
Serie		diately life-threatenin	a	03 Req 04 Pers	uired/p istent (	rolonge or signi	ed hospitalia ficant disab	zation ility /inca	pacity				05	Cong Othe	enital a r medica	noma Illy im	ly/bi porta	rth defect int serious e	vent
		ospitalized or v	-							nt? □I	No	ΠYe							
	•	Date Ad		-									-		arged				
		Day Mon		Year							[	Day		onth		ar			
				4				40 7	_										
5. V	vas iP/drug u	nder study adn	inis	terea/taker	n pric	or to t	inis ever		o ⊡Y .oratt			leas	e con	npieti		Secti n Tak			
			D	ate of Initial I	Dose	-	Date of D		Do		Route	•	Frequ	ency	with	Produ	uct		
															01 St Admin			Lot # and	Serial #
															02 Pe				
IP/A	mgen Device:		Da	y Month	Year	Day	Month	Year							discor 03 Wi				
																		Lot# Unknown	
																		Serial #	
																		🗌 Unavailab	(e/
< <ip< td=""><td>/Device&gt;&gt;</td><td>D blinded D open label</td><td></td><td></td><td></td><td>-</td><td></td><td></td><td></td><td></td><td></td><td>+</td><td></td><td></td><td></td><td></td><td>-+</td><td>Unknown</td><td></td></ip<>	/Device>>	D blinded D open label				-						+					-+	Unknown	
																		Lot # Unknown	
																		Serial #	
~10	/Device>>	D blinded D open label																Unavailab	le/
L DOIE	ILCONVERSE.	Li printand Li operi labeli							1									0.001010101	



AMGEN	Electronic Serious Adverse Event Contingency Report Form
Study # 20170173 AMG 397	For Restricted Use

	s	ite Nu	umber					Su	ıbject II	) Nun	nber						
6. CONCOMITANT MEDICATI							Med					yes, p	lease com	plete:			
Medication Name(s)		art Dat Nonth		Dey	Stop Mon	Date n v	ear		uspect Yær∕		ntinuing Yæs≁		Dose	Route		Treatr No√	nent Med Yær∕
												$\square$					
																	<u> </u>
7. RELEVANT MEDICAL HIS	TORY (i	inclu	de da	tes,	allei	rgies	; an	d an	y relev	ant p	prior ti	heraj	oy)				i
8. RELEVANT LABORATORY	Y VALU	ES (i	includ	de ba	seli	ne va	alue	es) A	ny Rele	evant	Laborat	tory v	alues? 🗆 I	No 🗆 Yes If	yes, pleas	e co	mplete:
Test																	
Unit Date																	
Day Month Year																	
																$\perp$	
9. OTHER RELEVANT TESTS	S (diagn	osti	cs an	d pro	ocea	lures	<i>;</i> )		Any C	)ther	Relevar	nt test	ts? □No	⊃ □ Yes If	yes, pleas	e co	mplete:
Date Dey Month Year		Addi	tional	Test	s							Res	ults			Units	3

FORM-056006

Page 2 of 3

Version 7.0 Effective Date: 1 February 2016



AMCEN	Electronic Serious Adverse Event Contingency Report Form
Study # 20170173 AMG 397	For Restricted Use

	Sit	e Nu	mber		Sub				lumber					
10. CASE DESCRIPTION (Provid	le na	rrati	ive det	ails of	feve	nts list	ed in a	secti	on 3)	Provid	e addi	itional pages if ne	ecessary. For each	
event in section 3, where relationsh	пр=т	es, j	please	provio	ie rat	ionale.								
Cinestus of Investigates on Designed								TW					Dete	
Signature of Investigator or Designee -								Title	2				Date	
I confirm by signing this report that the info causality assessments, is being provided to														
a Qualified Medical Person authorized by th							,							

FORM-056006

Page 3 of 3

Version 7.0 Effective Date: 1 February 2016



# Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN <sup>®</sup> Pregnancy Notification Worksheet											
Fa	x Completed For	n to the Country-	respective S								
1. Case Administrative Int Protocol/Study Number: AMG 39											
Study Design: 🗌 Interventional	Observational	(If Observational:	Prospective	Retrospective)							
2. Contact Information Investigator Name				Site #							
Phone () Institution	Fax (	)		Email							
Address         3. Subject Information         Subject ID #											
4. Amgen Product Expose	Ire										
Amgen Product	Dose at time of conception	Frequency	Route	Start Date							
				mm/dd/yyyy							
	r study drug) stop da	te: mm <u>//dd</u>		-							
If yes, provide product (or study drug) stop date: mm/dd/yyyy Did the subject withdraw from the study?   Yes   No 5. Pregnancy Information Pregnant female's LMP mm/ dd/ yyyy   Unknown Estimated date of delivery mm/ dd/ yyyy   Unknown   N/A If N/A, date of termination (actual or planned) mm/ dd/ yyyy Has the pregnant female already delivered?   Yes   No   Unknown   N/A If yes, provide date of delivery: mm/ dd/ yyyy Was the infant healthy?   Yes   No   Unknown   N/A If any Adverse Event was experienced by the infant, provide brief details:											

Form Completed by	
Print Name:	Title:
Signature:	Date:

**AMGEN**<sup>®</sup>

	AMGEN <sup>®</sup> Lactation Notification Worksheet											
Fax Completed Form to the	Country-respecti		<u>,</u>									
1. Case Administrative Inf												
Protocol/Study Number: AMG 39												
Study Design: Interventional		(If Observational:	Prospective	Retrospective)								
		(il observational L	Tropesse	[ Newspeaker								
2. Contact Information												
Investigator Name				Site #								
Phone () Fax () Email Institution												
Address												
3. Subject Information	Subject Date	of Disthermon	Inter (an									
Subject ID #	Subject Date	of Birth: mm	/ dd/ y	yyy								
4. Amgen Product Exposu	re											
	Dose at time of			21-12-1								
Amgen Product	breast feeding	Frequency	Route	Start Date								
				mm /dd /yyyy								
Was the Amgen product (or st	udy drug) discontinu	ued? 🗌 Yes 🗌 N	lo									
If yes, provide product (or	study drug) stop da	te: mm/dd	_/yyyy	_								
Did the subject withdraw from	the study? 🗌 Yes	No No										
5 Propot Cooding Informa	tion											
5. Breast Feeding Informa	uon											
Did the mother breastfeed or provid	de the infant with pu	mped breast milk whi	le actively tak	king an Amgen product? 🗌 Yes 🗌 No								
If No, provide stop date: m	m/dd	/yyyy										
Infant date of birth: mm/d	id/yyyy											
Infant gender: 🗌 Female 🗌 N	fale											
Is the infant healthy? Yes	No Unknown	N/A										
If any Adverse Event was experien	ced by the mother o	or the infant, provide b	rief details:									

Form Completed by:	
Print Name:	Title:
Signature:	Date:

.....

**AMGEN**<sup>®</sup>

# Appendix D. Operating Characteristics for 2-Parameter BLRM Design

The operating characteristics of the two-parameter BLRM design were evaluated via simulation. The cohort size was fixed to 2 or 4 subjects. The initial multiple subject dose level is 80 mg and subsequent doses were selected based on the following rules:

After each cohort, the next dose is the one with the highest probability of the target TPI, subject to the overdose control limits.

Dose escalation was stopped given 1 or more of the following conditions:

- There have been at least 6 subjects treated at the dose recommended by the model.
- A maximum number of 30 subjects are evaluated

A total of 6 dose levels (unit: mg) were considered: 80, 160, 240, 320, 480, 640 in these simulations of the multiple subject cohorts (80, 160, 320 and 640 are planned dose levels with 240 and 480 possible intermediate dose levels).

The design was evaluated for 3 possible dose-response scenarios: "Low", "Mid", and "High" MTD. Table 1 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 2 and Table 3 report the operating characteristics from 1,000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33]; Table 2 reports characteristics when the overdose control limit is 0.40 probability of an excessive or unacceptable TPI while Table 3 reports a limit of 0.25 probability of an excessive or unacceptable TPI.

Dose Level	80	160	240	320	480	640
MTD Scenario						
High	0.04	0.08	0.11	0.18	0.25	0.33
Mid	0.06	0.11	0.18	0.25	0.33	0.45
Low	0.09	0.18	0.25	0.33	0.45	0.55

Table 1. True Probability of DLT by Scenario for Simulated StudiesEstimating MTD

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

# Table 2. Operating Characteristics by Scenario for Simulated Studies Estimating<br/>the MTD When the Target TPI is (0.20, 0.33)Overdose Control Limit is 0.40 Probability of an Excessive or Unacceptable TPI

MTD Scenario	Hig	lh	Μ	lid	Lo	w
	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort
Number of Subjects	24	16	24	16	24	16
Median (IQR)	(20 to 28)	(12 to 18)	(20 to 28)	(14 to 18)	(20 to 28)	(14 to 18)
Number of DLTs	4	3	5	4	6	4
Median (IQR)	(3 to 5)	(2 to 4)	(4 to 6)	(3 to 5)	(4 to 7)	(3 to 6)
Proportion of DLT (%)	18	19	21	25	25	29
Median (IQR)	(13 to 21)	(14 to 25)	(19 to 25)	(19 to 29)	(21 to 30)	(25 to 33)
Percentage of studies re	commending d	ose with DLT p	probability of:			
≤ 10%	2.7	3.3	4.2	4.5	9.3	12.2
> 10% and ≤ 20%	23.4	19.7	12	10.7	17.5	13.5
> 20% and ≤ 33%	73.9	77.0	72.4	66.7	57.2	50.7
> 33%	0	0	11.4	18.1	16.0	23.6
Probability of identifying MTD to have 15% to 33% DLT probability	94.8	95.0	80.3	72.6	74.7	64.2

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval.

EAST version 6.4 software used to generate 1,000 simulated clinical trials for each scenario.

# Table 3. Operating Characteristics by Scenario for Simulated Studies Estimating<br/>the MTD When the Target TPI is (0.20, 0.33)Overdose Control Limit is 0.25 Probability of an Excessive or Unacceptable TPI

MTD Scenario	Hi	gh	Μ	lid	Lo	W
	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort
Number of Subjects	24	14	24	14	20	14
Median (IQR)	(20 to 28)	(12 to 16)	(20 to 28)	(12 to 18)	(16 to 24)	(10 to 18)
Number of DLTs	4	3	4	3	5	3
Median (IQR)	(3 to 5)	(2 to 3)	(3 to 6)	(2 to 4)	(4 to 6)	(2 to 5)
Proportion of DLT (%)	17	19	20	22	25	28
Median (IQR)	(13 to 21)	(14 to 25)	(17 to 25)	(18 to 29)	(20 to 29)	(22 to 36)
Percentage of studies reco	mmending do	se with DLT p	probability of:			
≤ 10%	4.7	10.7	5.3	15.5	16.9	28.9
> 10% and ≤ 20%	34.0	30.7	14.8	11.7	18.8	14.2
> 20% and ≤ 33%	61.3	58.6	72.2	67.7	54.5	42.7
> 33%	0	0	7.7	5.1	9.8	14.2
Probability of identifying MTD to have 15% to 33% DLT probability	93.5	87.9	79.9	72.9	73.3	56.9

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval.

EAST version 6.4 software used to generate 1,000 simulated clinical trials for each scenario.

Г

٦

Response	
Subcategory <sup>a</sup>	Multiple Myeloma Response Criteria
sCR⁵	CR as defined below and
	Normal SFLC ratio and
	<ul> <li>Absence of clonal cells in bone marrow<sup>c</sup> by immunohistochemistry or immunofluorescence<sup>c</sup></li> </ul>
CR⁵	Negative immunofixation on the serum and urine <u>and</u>
	Disappearance of any soft tissue plasmacytomas <u>and</u>
	<ul> <li>&lt; 5% plasma cells in bone marrow<sup>c</sup></li> </ul>
VGPR⁵	Serum and urine M-protein detectable by immunofixation but not on electrophoresis
	<u>or</u>
	<ul> <li>≥ 90% reduction in serum M-protein with urine M-protein level&lt; 100 mg/24 hours</li> </ul>
	<ul> <li>If the serum and urine M-protein are not measurable, a decrease of     ≥ 90% in the difference between the involved and uninvolved FLC levels     required in place of the M-protein criteria. However, documentation of     VGPR requires collection and analysis of 24 hour urine sample for UPEP     and immunofixation and confirmed to be negative.</li> </ul>
	<ul> <li>If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.</li> </ul>
PR⁵	<ul> <li>≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to &lt; 200 mg/ 24 h</li> </ul>
	<ul> <li>If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.</li> </ul>
	<ul> <li>If serum and urine M-protein are not measureable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow cell percentage was ≥ 30%</li> </ul>
	<ul> <li>If present at Baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required</li> </ul>
MR	<ul> <li>25%–49% reduction in the level of serum M-protein and a 50%–89% reduction in 24 hour urinary M-protein, which still exceeds 200 mg per 24 hours</li> </ul>
	• If the serum and urine M-protein are not measurable, a decrease of 25%-49% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.
	<ul> <li>If present at Baseline, a 25%–49% reduction in the size of soft tissue plasmacytomas is also required</li> </ul>
Stable disease	<ul> <li>Not meeting criteria for CR, VGPR, PR, or PD</li> </ul>

# Appendix E. International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (IMWG-URC)

Footnotes defined on next page

Page 1 of 2



Response	
Subcategory <sup>a</sup>	Multiple Myeloma Response Criteria
PD⁵	Any one or more of the following:
	<ul> <li>Increase of ≥ 25% from lowest response value in:</li> </ul>
	<ul> <li>Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)</li> </ul>
	<ul> <li>O Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)</li> </ul>
	<ul> <li>Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be &gt;10 mg/dL</li> </ul>
	<ul> <li>➢ Bone marrow plasma cell percentages (absolute percentage must be ≥ 10%)</li> </ul>
	<ul> <li>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<sup>e, f, g</sup></li> </ul>
	<ul> <li>Development of hypercalcemia (corrected serum calcium &gt; 11.5 mg/dL or 2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder</li> </ul>

Page 2 of 2

Source: Durie 2006; Rajkumar 2011 (modified for protocol purposes).

CR = complete response; sCR = stringent complete response; FLC = serum light chain; MR = minor response; PD = progressive disease; PR = partial response; SFLC = serum free light chain; VGPR = very good partial response

- **Note**: Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted criteria for PD only needs to be met, and confirmed, in 1 parameter. For patients without measurable protein on UPEP at Baseline, UPEP will need to be repeated to confirm a response.
  - <sup>a</sup> Patients with measurable disease in both serum (SPEP) and urine (UPEP) at study entry are required to meet response criteria in both UPEP and SPEP in order to qualify for a MR or better. Conversely, it should be noted that criteria for PD only needs to be met, and confirmed, in one parameter.
  - <sup>b</sup> All response categories (CR, sCR, VGPR, PR) require 2 consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow, plasmacytoma, and skeletal survey assessments are not required to be confirmed by repeat testing. SD requires a duration of ≥ 6 weeks.
  - <sup>c</sup> Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.</p>
  - <sup>d</sup> **Determination of PD while on study requires 2 consecutive assessments** made at any time before classification of PD and/or the institution of new therapy. Serum M-component increases of ≥ 1 g/dL from nadir are sufficient to define progression if nadir M-component is ≥ 5 g/dL.
  - Plasmacytomas: A definite increase in the size is defined as a ≥ 50% increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm<sup>2</sup>. Plasmacytomas of lesser size will be considered non-measurable.
  - <sup>f</sup> The requirement for bi-directional measurements applies only to plasmacytomas.
  - <sup>g</sup> The plasmacytoma specifications for PD are based on interpretation of the IMWG-URC and practical considerations for study execution.



# Appendix F. ECOG Performance Status and NYHA Classification

# Eastern Cooperative Oncology Group (ECOG) Performance Status

- 0. Fully active, able to carry on all pre-disease performance without restriction
- 1. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
- 2. Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4. Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair
- 5. Dead

# New York Heart Association Functional Classification

- 1. Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
- 2. Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
- 3. Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
- 4. Class IV Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

# Appendix G. Definition of Relapsed or Refractory Progressive Disease and Line of Therapies

Relapsed disease is defined as progression occurs in the absence of therapy.

**Refractory disease** is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.

**Progressive Disease for patients with Multiple Myeloma** requires any one or more of the following:

- Increase of ≥ 25% from lowest response value in any of the following
  - Serum M-component and/or (the absolute increase must be  $\ge$  0.5 g/dl)
  - O Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (the absolute increase must be > 10 mg/dl)
  - Bone marrow plasma cell percentage: the absolute % must be > 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease (Rajkumar, 2011).

# Progressive disease in patients with AML is defined as:

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:



- > 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (> 0.5 x 10<sup>9</sup>/L [500/uL], and/or platelet count to > 50 x 10<sup>9</sup>/L [50,000/uL] nontransfused); or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10<sup>9</sup>/L (>25,000/uL) (in the absence of differentiation syndrome)<sup>†</sup>; or
- New extramedullary disease

# Relapse after complete remission for patients with AML is defined as:

- Bone marrow blasts  $\geq$  5%; or
- reappearance of blasts in the blood; or
- development of extramedullary disease

These response criteria were published in 2010, "Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European Leukemia Net" (Döhner et al, 2010).

The criteria for progressive disease were suggested in the 2017 ELN recommendations (Döhner et al, 2017).

# Appendix H. World Health Organization Classification for Acute Myeloid Leukemia

Definition AML: ≥ 20% myeloblasts in blood or in bone marrow

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. **Patients with APML are not eligible for this study.** First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized. Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (Arber et.al, 2016).

AML and related neoplasms	
AML with recurrent genetic abnormalition	esAML with t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i>
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);
	CBFB-MYH11
	Acute promyelocytic leukemia with PML-RARA*
	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A†
	AML with t(6;9)(p23;q34.1); DEK-NUP214
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);
	RBM15-MKL1‡
	Provisional entity: AML with BCR-ABL1
	AML with mutated NPM1§
	AML with biallelic mutations of CEBPA§
	Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes	
Therapy-related myeloid neoplasms{	
AML, NOS	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia #
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis

Footnotes defined on next page



Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemias of ambiguous lineage	Acute undifferentiated leukemia MPAL with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i> ** MPAL with t(v;11q23.3); <i>KMT2A</i> rearranged MPAL, B/myeloid, NOS MPAL, T/myeloid, NOS

For a diagnosis of AML, a marrow blast count of  $\geq$ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16). Adapted from Arber et al. MPAL, mixed phenotype acute leukemia; NK, natural killer.

\* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12);*NUMA1-RARA*; AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5B-RARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

<sup>†</sup> Other translocations involving *KMT2A* (MLL) should be reported accordingly: for example, AML with t(6;11)(q27;q23.3); *MLLT4-KMT2A*; AML with t(11;19)(q23.3;p13.3); *KMT2A-MLLT*1; AML with t(11;19)(q23.3;p13.1); *KMT2A-ELL*; AML with t(10;11)(p12;q23.3); *MLLT10-KMT2A*.

‡ Rare leukemia most commonly occurring in infants.

§ Diagnosis is made irrespective of the presence or absence of multilineage dysplasia.

|| At least 20% (≥20%) blood or marrow blasts AND any of the following: previous history of MDS or MDS/MPN; myelodysplasia-related cytogenetic abnormality (see list below); multilineage dysplasia; AND absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities. Cytogenetic

abnormalities sufficient to diagnose AML with myelodysplasia-related changes are: Complex karyotype (defined as 3 or more chromosomal abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCRABL1); Unbalanced abnormalities: 27 or del(7q); 25 or del(5q); i(17q) or t(17p); 213 or del(13q); del(11q); del(12p) or t(12p); idic(X)(q13); Balanced abnormalities: t(11;16)(q23.3;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.2); t(2;11)(p21;q23.3); t(5;12)(q32;p13.2); t(5;7)(q32;q11.2); t(5;17)(q32;p13.2); t(5;10)(q32;q21.2); t(3;5)(q25.3;q35.1).

{ Cases should be classified with the related genetic abnormality given in the diagnosis.

# The former subgroup of acute erythroid leukemia, erythroid/myeloid type ( $\geq$ 50% bone marrow erythroid precursors and  $\geq$ 20% myeloblasts among nonerythroid cells) was removed; myeloblasts are now always counted as percentage of total marrow cells. The remaining subcategory AML, NOS, pure erythroid leukemia requires the presence of >80% immature erythroid precursors with  $\geq$ 30% proerythroblasts. \*\* *BCR-ABL1* leukemia may present as MPAL; treatment should include a tyrosine kinase inhibitor.

### Appendix I. Response Assessment per the Lugano Classification for NHL

- 5- point scale (Deauville)
- 1. no uptake above background;
- 2. uptake ≤ mediastinum;
- 3. uptake > mediastinum but ≤ liver;
- 4. uptake moderately > liver;
- 5. uptake markedly higher than liver and/or new lesions;
- X. new areas of uptake unlikely to be related to lymphoma.

Response	Compete Response	Partial Response	Stable Disease	Progressive Disease
PET/CT Response	Complete Metabolic Response	Partial Metabolic Response	No Metabolic Response	Progressive Metabolic Disease
Target Masses	Score 1, 2, or 3 with or without a residual mass	Score 4 or 5 reduced uptake compared with baseline residual mass(es) of any size	Score 4 or 5 no significant change in FDG uptake from baseline	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma
New Lesions	None	None	None	New FDG-avid foci consistent with lymphoma rather than another etiology
Bone Marrow	No FDG avid focal lesions	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	No change from baseline	New or recurrent FDG-avid foci



Category	Definition	Comment
Response		
<ul> <li>CR without minimal residual disease (CR<sub>MRD</sub>-)</li> </ul>	If studied pretreatment, CR with negativity for a genetic marker	Sensitivities vary by marker tested, and by method used; therefore,
	by RT-qPCR, or CR with negativity by MFC	test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\ge$ 1.0 x 10 <sup>9</sup> /L (1000/uL); platelet count $\ge$ 100 x 10 <sup>9</sup> /L (100,000/uL)	MRD⁺ or unknown
<ul> <li>CR with incomplete hematologic recovery (CRi)</li> </ul>	All CR criteria except for residual neutropenia (<1.0 x 10 <sup>9</sup> /L [1000/uL]) or thrombocytopenia (<100 x 10 <sup>9</sup> /L [100,000/uL])	
<ul> <li>Morphologic leukemia-free state (MLFS)</li> </ul>	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
<ul> <li>Partial remission (PR)</li> </ul>	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
<ul> <li>Primary refractory disease</li> </ul>	No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
<ul> <li>Death in aplasia</li> </ul>	Deaths occurring ≥ 7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
<ul> <li>Death from indeterminate cause</li> </ul>	Deaths occurring before completion of therapy, or < 7 d following its completion; or deaths occurring ≥ 7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	

Footnotes defined on next page

Page 1 of 2



Category	Definition	Comment
Response criteria for clinical trials only		
Stable disease	Absence of CR <sub>MRD-</sub> , CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
<ul> <li>Progressive disease (PD)*,†</li> </ul>	Evidence for an increase in bone marrow blast percentage	Category mainly applies for older patient given low intensity
	and/or increase of absolute blast counts in the blood:	or single-agent "targeted therapies" in clinical trials. In general, at least 2 cycles of a novel agent should be
	<ul> <li>&gt;50% increase in marrow blasts over baseline (a minimum</li> </ul>	administered. Some protocols may require blast increase in 2 consecutive
	15% point increase is required in cases with < 30% blasts at	marrow
	baseline; or persistent marrow blast percentage of > 70%	assessments at least 4 wk apart; the date of progression should
	over at least 3 mo; without at least a 100% improvement in	then be defined as of the first observation date.
	ANC to an absolute level (> 0.5 x 10 <sup>9</sup> /L [500/uL], and/or	
	platelet count to > 50 x 10 <sup>9</sup> /L [50,000/uL] nontransfused); or	Some protocols may allow transient addition of hydroxyurea to
	$\bullet$ > 50% increase in peripheral blasts (WBC x % blasts) to	lower blast counts. "Progressive disease" is usually accompanied by a decline in
	<ul> <li>&gt; 25 x 10<sup>9</sup>/L (&gt;25,000/uL) (in the absence of differentiation syndrome)†; or</li> <li>New extramedullary disease</li> </ul>	ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.
Relapse	,	'
Hematologic relapse	Bone marrow blasts $\geq$ 5%; or reappearance of blasts in the	
(after CR <sub>MRD-</sub> , CR, CRi)	blood; or development of extramedullary disease	Test applied, sensitivity of the assay, and cutoff values used
Molecular relapse	If studied pretreatment, reoccurrence of MRD as assessed by	must be
(after CR <sub>MRD-</sub> )	RT-qPCR or by MFC	reported; analyses should be done in experienced laboratories (centralized diagnostics)

Page 2 of 2

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

\* The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

† Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.



			(	Grade		
Complication	0	1	2	3	4	5
Creatinine*, <sup>†</sup>	≤1.5 × ULN	1.5 × ULN	1.5 - 3.0 × ULN	> 3.0 - 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	intervention incompletely ( indicated controlled medically or controlled with		Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	-	O Lie Ci		Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

# Appendix K. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Element	Value		Change from Baseline
Uric Acid	≥ 476 µmol/L (8 mg/dL)	-OR-	25% increase from baseline
Potassium	$\geq$ 6.0 mmol/L (6 mg/L)	-OR-	25% increase from baseline
Inorganic phosphorus	$\geq$ 1.45 mmol/L (4.5 mg/dL)	-OR-	25% increase from baseline
Calcium	$\leq$ 1.75 mmol/L (7.0 mg/dL)	-OR-	25% decrease from baseline

# Appendix L. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Note: Two or more elements with laboratory values out of range or changes from baseline.



# Protocol Title: A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects With Selected Relapsed or Refractory Hematological Malignancies

# AMG 397

Amgen Protocol Number AMG 397 20170173

Amendment Date: 28 March 2018

# Rationale:

The following updates were made to the protocol, dated 28 March 2018:

- Addressed the following changes requested by FDA:
  - Changes to inclusion/exclusion criteria
  - o Definition of DLT and criteria for DLT
  - Extended DLT window from 21 days to 28 days
  - Added safety monitoring assessments including:
    - Cardiac echocardiogram, imaging and assessments if any clinical signs or symptoms of cardiomyopathy or cardiac compromise are noted
  - Inclusion of an MRI/CT at baseline to check for CNS lymphoma or uncontrolled CNS disease
- Begin enrollment of Cohort 1B (AML) at the same time as Cohort 1A at the same doses
- Implement measures to mitigate the risk and manage tumor lysis syndrome including below:
  - Every subject will receive mandatory prophylaxis for tumor lysis syndrome (TLS) prior to the first dose of AMG 397 and prior to at all subsequent dose escalations
  - Allopurinol should be used to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase, may be used per PI discretion and the Institutional guidelines.
  - Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.</li>



- Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared
- Typographical errors and inconsistencies between sections throughout the protocol were corrected.

# **Description of Changes:**

# 1. Title Page

Removed strikethrough text, Added text in BOLD		
Clinical Study Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805-447-1000	
Key Sponsor Contacts:	MD Early Development Lead Phone: E-mail:	
	Clinical Research Study Manager Phone: E-mail:	
Date:	30 November 2017	
Amendment 1	28 March 2018	

# 2. Investigator's Agreement, page 2

Removed strikethrough text, Added text in BOLD

# Investigator's Agreement

I have read the attached protocol entitled "A Phase 1 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of AMG 397 in Subjects with Selected Relapsed or Refractory Hematological Malignancies", dated 30 November 201728 March 2018, and agree to abide by all provisions set forth therein.



# 3. Protocol Synopsis; Primary Objectives, Exploratory Objectives

# Added text in **BOLD**

#### Primary Objectives:

- Evaluate the safety and tolerability of AMG 397
- Estimate the maximum tolerated doses (MTDs) and/or biologically active doses (eg, recommended phase 2 doses [RP2Ds]) of AMG 397

#### Secondary Objectives:

- Evaluate the efficacy of AMG 397
- Evaluate the pharmacokinetics (PK) of AMG 397

#### Exploratory Objectives:

- Explore pharmacokinetic/pharmacodynamic (PK/PD) relationships for safety and/or efficacy endpoints
- · Identify metabolite(s) of AMG 397 in plasma and urine
- Demonstrate AMG 397 inactivation of myeloid cell leukemia sequence 1 (MCL1) by the activation of BAX and caspase 3 in circulating monocytes or blast cells, and/or the decrease of circulating monocytes
- Evaluate patient responses according to disease-specific features in tumor cells such as chromosomal amplifications, rearrangements, gene expression profiles, protein expression as well as somatic mutations as necessary
- · Evaluate changes to immune cell subsets in peripheral blood due to MCL1 inactivation
- Assess Minimal Residual Disease (MRD) status with patient response as necessary



# 4. Protocol Synopsis; Study Design; 4<sup>th</sup> paragraph,

# Removed strikethrough text, Added text in BOLD

#### Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study evaluating AMG 397 administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle in adult subjects with selected RR hematological malignancies.

This study will consist of dose escalation (Part 1) to evaluate safety and tolerability and estimate the MTD/RP2D of AMG 397 using a Bayesian Logistic Regression Model (BLRM) in the following groups:

- Group 1A will consist of subjects with RR MM and/or NHL
- Group 1B will consist of subjects with RR AML

This will be followed by a dose expansion (Part 2) to gain further efficacy and safety experience with AMG 397 in adult subjects with RR MM, DLBCL, and AML.

The study will be conducted at up to 20 sites **globally** in Australia, Canada, FranceEurope, Japan, and the United States (US). Other countries or regions may be added.

#### Dose Escalation-Part 1

Dose escalation will estimate MTDs for Groups 1A and Group 1B using an adaptive, BLRM design. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on dose escalation/change. The table below shows the planned dose levels for dose escalation.

Dose Cohort Levels	Dose (mg)
1	80
2	160
3	320
4	640

#### Planned Doses per Dose Cohort Level

Dose escalation will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg with enrollment from Group 1A and 1B. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 281 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.



Dose escalation for Group 1B is anticipated to begin after at least one cohort from Group 1A completes the safety review for the DLT period. The starting dose level for Group 1B will be at the highest dose level from Group 1A, which the DLRT deems safe and tolerable.

Dose escalation for both Group 1A and 1B will continue until any of the following events:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

There is a potential for tumor lysis syndrome (TLS) in subjects with hematologic malignancies, especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS:

- Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397.
- Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.
- For the management of TLS, please refer to Section 6.5.7 for more details

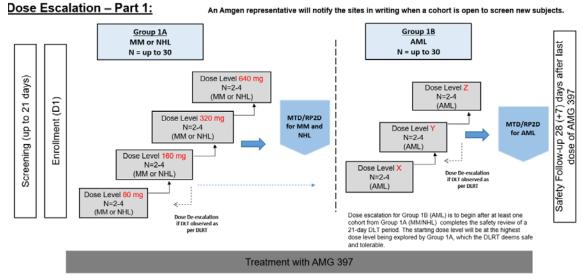
The DLRT will convene to review the safety data and may determine a lead-in dose which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

NOTE: Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

# 5. Protocol Synopsis; Study Design and Treatment Schema

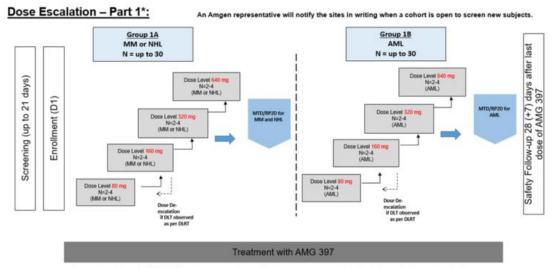
# Removed old figure:



4-week cycles of AMG 397 until progression of disease, unacceptable toxicity, withdrawal or death

# Replaced Figure with Below:

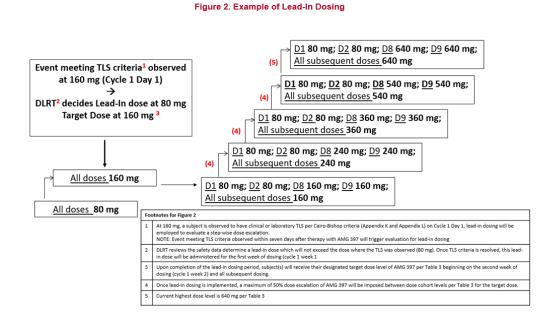
#### Study Design and Treatment Schema



4-week cycles of AMG 397 until progression of disease, unacceptable toxicity, withdrawal or death \*No lead-in dosing is implemented

# 6. Protocol Synopsis; Study Design and Treatment Schema

# Added Figure 2:



# 7. Section 2.1.1 Multiple Myeloma Background, full Section

# Removed strikethrough text, Added text in BOLD

Multiple myeloma is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, production of a monoclonal protein present in the blood or urine and associated organ dysfunction (Palumbo and Anderson 2011).

Multiple myeloma is the second most common (10-15%) of all hematological cancer. It is responsible for 15-20% of all deaths from hematological cancer and about 2% of all cancer deaths. Recent improved understanding of the pathogenesis of myeloma has led to the development of new treatments. Survival is improving, with median overall survival in the range of 7-10 years after initial diagnosis. Nevertheless, myeloma remains an incurable cancer, and with subsequent relapses, the disease becomes refractory to current treatments. Therefore, RR multiple myeloma is still an unmet medical need (Smith and Yong 2013).



Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-center B cells. Multistep genetic and micro-environmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma (Palumbo and Anderson, 2011).

The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production, and renal insufficiency (Durie, 2011). Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only-clinical observation, since early treatment with conventional chemotherapy has shown no benefit. Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma. The treatment strategy is mainly related to age. Current data would support the initiation of induction therapy with thalidomide. lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for subjects under the age of 65 years who do not have substantial heart, lung, renal, or liver dysfunction. Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older subjects or those with coexisting conditions. Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in subjects older than 65 years of age. Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in subjects over 75 years of age or in younger subjects with coexisting conditions. Biologic age, which may differ from chronologic age, and the presence of coexisting conditions should determine treatment choice and drug dose (Palumbo and Anderson, 2011).

Treatment of RR MM presents a special therapeutic challenge, due to the heterogeneity of disease at relapse and the absence of clear biological based recommendations regarding the choice of salvage therapies at various time points of disease progression. With increasing recognition of the inherent clonal heterogeneity and genomic instability of the plasma cells influencing both inherent and acquired therapeutic resistance, the identification of the optimal choice and sequence of therapies has become critical.

Several new agents and targets are currently under development and show considerable promise. Besides-In the past 5 years, carfilzomib,-and-pPomalidomide, elotuzumab, ixazomib, daratumumab, that-were granted approval by US FDA in 2012 and 2013 respectively for RR MM. , the next generation proteasome inhibitors (PIs) (ixazomib, marizomib and oprozomib), other molecularly targeted therapies directed at specific cell signaling pathways (including histone deacetylase inhibitors, PI3K/AKT/mTOR inhibitors, Hsp90 inhibitors, cell cycle inhibitors, kinesin spindle protein inhibitors) are currently in development. Even newer approaches such as monoclonal antibodies targeting SLAME7, CD38, CD138, and others have also demonstrated promising-anti-myeloma activity (Nooka, 2014). Despite advances in the management of multiple myeloma, however, -as described, relapse is inevitable in almost all subjects. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival (Dimopoulos, 2015). Thus, there remains an urgent need for treatment options for patients with RR MM. More treatment options are still warranted.

#### 8. Section 2.1.2 Non-Hodgkin's Lymphoma Background, first paragraph

#### Removed strikethrough text, Added text in BOLD

About 74,680 people (41,730 males and 32,950 females) will be diagnosed with Non Hodgkin's Lymphoma (NHL), and about 19,910 people will die from this malignancy. The annual incidence of Non Hodgkin's Lymphoma (NHL) in Europe and the United States is estimated to be 15 to 20 cases/100,000 (Fisher and Fisher, 2004). Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for 30% to 40% of cases and 13% of all hematologic disorders. The incidence is approximately 8 cases per 100,000 and rises with age; the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Morphologically similar entities have historically been treated in a similar manner as DLBCL, and thus are collectively known as aggressive B-cell lymphomas. DLBCL as a uniform diagnostic entity, makes up approximately 85% of aggressive B-cell lymphomas (Ziepert et al. 2010). However, distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications (Swerdlow et al. 2016). Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975). Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015). Patients with DLBCL who do not respond to

# Page 11 of 56

# 9. Section 2.2.3 Pharmacokinetics, second paragraph

# Removed strikethrough text, Added text in BOLD

AMG 397 was an inducer of CYP2B6, CYP2C9, and CYP3A4, and reversible inhibitor of CYP2B6, CYP2C8, and CYP3A4 in vitro while it was not an inhibitor of other major drug metabolizing human CYP enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. AMG 397 was also a time-dependent inhibitor of CYP3A4 but not of any of the other CYPs tested. Additionally, AMG 397 was identified as an inhibitor of P-gp (IC<sub>50</sub> of 8.7 µM). For BCRP, MATE1, MATE2-K, and OATP1B1, incomplete inhibition (36 – 54%) was observed at the highest test concentration (100 µM) of AMG 397, suggesting weak inhibition. At the highest test concentration (100 µM) of AMG 397, incomplete inhibition was observed for additional transporters; BCRP (51%), MATE1 (54%), MATE2 K (48%), and OATP1B1 (36%). AMG 397 was not an inhibitor of OATP1B3, OAT1, OAT3, OCT1, or OCT2. Considering dose levels and dosing frequency, and based on physiologically based pharmacokinetic modelling, it was determined that AMG 397 has a potential to interact with CYP3A4 and P-gp.

### 10. Section 2.2.4 AMG 397 Preclinical Toxicology, last paragraph

#### Added text in **BOLD**

#### Tumor Lysis Syndrome

Tumor lysis syndrome has been observed in a clinical trial with a drug of the same mechanism of action (AMG 176). Administration of AMG 176 has been associated with tumor lysis syndrome with fatal outcome. Subjects with a high tumor burden or compromised renal function (eg, International Staging System [ISS] Stage II/III) may be at elevated risk for tumor lysis syndrome.

Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed in all subjects and any pre-existing abnormalities must be corrected prior to starting treatment with AMG 397. In addition, subjects must be appropriately hydrated prior to each dose of AMG 397. Further details regarding mandatory tumor lysis syndrome prophylaxis are provided in the study protocol in Section 6.5.7.



# 11. Section 3.1 Study Design; Dose Escalation – Part 1

Removed strikethrough text, Added text in BOLD

### Dose Escalation-Part 1

During dose escalation (Part 1) AMG 397 will be administered orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28day treatment cycle.

Dose escalation will estimate MTDs for Group 1A and Group 1B using an adaptive, BLRM design. Table 3 shows the planned dose levels for dose escalation. The Dose Level Review Team (DLRT) will review data, monitor safety, and make decisions on any dose escalation/change. For more details regarding the dose escalation, please see Section 6.2.1.2.

Dose Cohort Levels	Dose (mg) PO
1	80
2	160
3	320
4	640

Table 3. Planned Doses per Dose Cohort Level

Dose escalation for Group **1a1A and Group 1B** will begin with 2-4 subjects treated at the lowest planned dose level of 80 mg. Dose escalation will follow the planned schedule described above with 2-4 subjects treated in each cohort.

DLRT will convene to review the safety data and determine the appropriate dose to be implemented. Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity. Skipping of planned dose levels is not allowed. Dose escalation decisions will not be made until all subjects in a cohort(s) are monitored through the DLT-observation period of 21-28 days following treatment initiation. Intermediate dose levels and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data per the decision of the DLRT.



Dose escalation for Group 1B is anticipated to begin after at least one cohort from Group 1A completes the safety review for the DLT period. The starting dose level for Group 1B will be at the highest dose level from Group 1A, which the DLRT deems safe and tolerable.

Dose escalation for both Group 1A and 1B **respectively**, will continue until any of the following events:

- The highest planned dose level for each group is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

Intermediate doses and alternative dosing schedule(s) may be explored based on emerging pharmacokinetic and safety data as decided by the DLRT.

#### Lead-in Dosing

Due to the potential risk of TLS for subjects affected by hematologic malignancies, it is anticipated that lead-in dosing may be implemented. At any point during the study, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed within seven days after therapy with AMG 397, lead-in dosing may be initiated to evaluate a stepwise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing. See Section 6.2.1.1.1 for more details

# 12. Section 3.2; Number of Sites

This study will be conducted at up to 20 sites **globally** in Australia, Canada, FranceEurope, Japan and the United States the United States. Additional regions, countries, or sites may be added.

Sites that do not enroll subjects into an open cohort within 4 months of site initiation during dose escalation or expansion may be closed or replaced.

# 13. Section 3.4; Replacement of Subjects

# Removed strikethrough text, Added text in BOLD

During dose escalation, subject(s) that are not DLT evaluable may be replaced if:

- <u>A-subject is nSubject(s) is notet DLT-evaluable</u>. See Section 6.2.1.2 for definition of DLT-evaluable
- if the sSubject(s) discontinues treatment for any reason other than a DLT during the DLT-observation period prior to completing the first 21 days of AMG 397 treatment.

Additional subjects may **also** be enrolled if Amgen's medical monitor determines that the minimum required number(s) of evaluable subjects have not been enrolled in each cohort.



#### 14. Section 4.1; Inclusion Criteria

#### Removed strikethrough text, Added text in BOLD

#### 4. SUBJECT ELIGIBILITY

#### 4.1 Inclusion Criteria

- Subject has provided informed consent prior to initiation of any study-specific activities/procedures.
- 102. Age ≥ 18 years old
- 103. Pathologically-documented, definitively-diagnosed relapsed or refractory MM, NHL, or AML (Appendix GAppendix G) for and is intolerant to, or considered ineligible for available therapies known to provide clinical benefit.

103. which no standard therapy is available or the subject refuses standard therapy

#### 104. MM subjects only:

- Measurable disease per the IMWG response criteria (Appendix EAppendix E; assessed within 21 days prior to enrollment), as indicated by one or more of the following:
  - Serum M-protein ≥ 0.5 g/dL
  - Origination of the protein ≥ 200 mg/24 hours
  - For Subjects who do not meet 1 of the 2 prior criteria:
    - Serum Free Light Chain (sFLC) ≥ 10 mg/dL (≥ 100 mg/L) andAND an abnormal sFLC ratio (< 0.26 or > 1.65) as per the IMWG response criteria

#### 105. NHL subjects only:

 Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension

#### 106. AML subjects only:

- Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix HAppendix H)
- More than 5% blasts in bone marrow



## 15. Section 4.1 Inclusion Criteria; Additional criteria for Part 2 – Dose Expansion Subjects

Removed strikethrough text, Added text in BOLD

### Additional criteria for Part 2 - Dose Expansion subjects

#### 114. MM subjects only

 Pathologically documented, definitively diagnosed, relapsed or refractory disease following at least 32 lines of therapy including but not limited to a proteasome inhibitor, an immunomodulatory agent and/or CD38-targeted immunochemotherapy.

**NOTE:** The investigator must be of the opinion that no other treatment option will result in a durable response.

#### 115. NHL subjects only

 Pathologically confirmed de novo DLBCL, or DLBCL who have failed at least two prior therapies transformed from previously diagnosed indolent lymphoma following front line treatment of standard multiagent chemotherapy containing an anthracycline AND an approved anti CD20 agent. Examples of appropriate therapy include but are not limited to R CHOP (14 or 21), R CHOEP, and DA R EOCH.

**NOTE:** For subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy.

#### 116. AML subjects only

 Pathologically confirmed diagnosis of AML as defined by the WHO Classification (Appendix HAppendix H) persisting or recurring following no more than 2 lines of prior therapies



#### 16. Section 4.2 Exclusion Criteria

#### Removed strikethrough text, Added text in BOLD

#### 4.2 Exclusion Criteria

201. Previously received an allogeneic stem cell transplant within 6 months of study day 1 OR having signs or symptoms of acute or chronic graft-versus-host disease

202. Autologous stem cell transplant < 90 days prior to study day 1

# 202.203. Candidates for stem cell transplant should have failed or are not considered eligible for either allogeneic and autologous transplant

203.204. History of other malignancy except:

- Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- · Adequately treated cervical carcinoma in situ without evidence of disease
- · Adequately treated breast ductal carcinoma in situ without evidence of disease
- · Prostatic intraepithelial neoplasia without evidence of prostate cancer
- · Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

#### 205. Myocardial infarction within 6 months of study day 1

- 204.206. Symptomatic congestive heart failure (New York Heart Association > Class II) (Appendix FAppendix F)
- 205.207. History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 6 months prior to study day 1
- 206.208. Uncontrolled active linfection requiring intravenous anti-infective treatments within 1 week of study day 1
- 207.209. Known positive results for human immunodeficiency virus (HIV)



### 17. Section 4.2 Exclusion Criteria; pages 45-47

#### Removed strikethrough text, Added text in BOLD

214. Males and females of reproductive potential who are unwilling to practice an acceptable method(s) of effective birth control while on study through 3 months after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with barrier methods (diaphragm, cervical cap, or cervical sponge), hormonal birth control or IUD (females).

NOTE: A woman is considered of childbearing potential (WOCBP), (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- 213.215. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 3 months after receiving the last dose of study drug.
- 218.220. Use of herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days14 days prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- 227. NHL subjects with the following criteria are excluded:
- CNS lymphoma or evidence of uncontrolled CNS disease
- Burkitt's lymphoma
- Lymphoblastic lymphoma

#### 225.228. AML subjects with any of the following criteria are excluded:

- Circulating white blood cells > 25,000 /µl. Hydroxyurea to control peripheral blood leukemic cell counts, within 24 hours of study day 1 is permitted.
- Promyelocitic leukemia



#### 18. Section 6.2.1.1 Dosage, Administration and Schedule

#### Removed strikethrough text, Added text in BOLD

During dose escalation (Part 1), and dose expansion (Part 2) AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. Table 3 shows the planned dose levels for dose escalation.

2 On days especially when PK samples will be taken, doses will be administered in clinic. Subjects will self administer AMG 397 on all other days.

The planned dose levels for escalation are 80, 160, 320, and 640 mg. During dose expansion (Part 2) AMG 397 will be given orally once daily for 2 consecutive days followed by 5 days break at a weekly interval, as part of a 28-day treatment cycle. The planned dose level(s) for dose expansion will be determined based on data collected during dose escalation.



On days of hospitalization and during clinic visits, doses will be administered at the clinic. Subjects will self-administer AMG 397 on all other designated timepoints per Table 4 and 5 on days without clinic visits.

AMG 397 can be taken with or without food (i.e., subjects may choose to eat prior to or after taking study drug). A missed dose will not be made up. The tablet should be swallowed whole without crushing or breaking. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Subjects will be asked to record the date, time, and number of tablets consumed in a subject drug diary that must be brought to each study visit and will be reviewed by study staff. The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).

The amount dispensed, amount returned, date dispensed, date returned, **and** lot number of AMG 397 are to be recorded in the site's drug accountability log for each subject. The amount dosed, lot number of IP, and start date will be recorded on each subject's eCRF(s).Please refer to the Investigational Product Instructional Manual for more details on dosage, administration and schedule of AMG 397.

#### Pre-dosing considerations for AMG-397

No routine pre-medication should be administered prior to the first dose of AMG 307. If a subject develops a reaction, subjects should acutely be treated according to best clinical practice. Medication may be administered as deemed appropriate by the investigator to control any reactions according to best clinical practice. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. All medication and symptoms should be documented in the eCRF. Amgen must be notified within 24 hours when a subject has had  $\geq$  Grade 3 AE.

The effects of overdose of this product are not known.



#### 19. Section 6.2.1.1.1 Lead-in Dosing

#### Removed strikethrough text, Added text in BOLD

There is a potential for tumor lysis syndrome (TLS) in subjects affected by hematologic malignancies especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk of TLS, tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to any dose escalation (Section 6.5.7).

Additionally, when an event meeting clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and Appendix L) is observed, lead-in dosing may be initiated to evaluate a step-wise dose escalation for all subsequent dosing. See Figure 2 for an example of lead-in dosing.

The DLRT will convene to review the safety data and may determine a lead-in dose which will not exceed the dose where the TLS was observed. Once TLS criteria is resolved, this lead-in dose will be administered for the first week of dosing (cycle 1 week 1). Upon completion of the lead-in dosing period, subject(s) will receive their designated target dose level of AMG 397 per Table 3 beginning on the second week of dosing (cycle 1 week 2) and all subsequent dosing.

NOTE: Once lead-in dosing is implemented, a maximum of 50% dose escalation of AMG 397 will be imposed between dose cohort levels per Table 3 for the target dose.

Once lead-in dosing is initiated, additional monitoring of electrolyte values is required prior to dosing at the following times (see Table 4 and Table 5):

- Prior to the Week 1, Day 1 Dose
- · Prior to each dose during the Lead-in Period
- Prior to the initial dosing at the target dose level

Prior to administering AMG 397, all electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be within normal range.

NOTE: Laboratory value changes must be confirmed by another laboratory test (1-2 hours later) prior to assigning a TLS grade.

Dose Adjustments for Lead-In Dosing

Evidence of TLS will be carefully monitored on study and AMG 397 will be held until resolution of TLS abnormalities. Following lead-in dosing of AMG 397, if one or more Cairo-Bishop criteria is met (See Appendix K and Appendix L), no additional AMG 397 doses will be administered until it is resolved (eg, laboratory values are no longer within range of the values stated in Appendix K and Appendix L). Upon resolution, the subject will repeat the lead-in dosing for an additional week prior to receiving the target dose.

NOTE: Lead-in dosing will be repeated if the subject is observed to meet one or more of the Cairo-Bishop criteria post-dose.

Decisions to modify the AMG 397 lead-in dosing period regimen, lead-in period starting dose, and dosing increments, will be made in conjunction with the investigator and Amgen medical monitor and communicated to the IRB/EC, as appropriate.

#### 20. Section 6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

#### Removed strikethrough text, Added text in BOLD

#### 6.2.1.2 Dose-cohort Study Escalation and Stopping Rules

The Dose Level Review Team (DLRT) will convene before decisions to dose escalate or de-escalate is made or when cohorts are suspended per protocol. The DLRT will be composed of select Investigator(s), Amgen medical monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager (CRSM) and Biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacologist). The DLRT voting members include the Amgen Medical Monitor and Global Safety Officer or designee, in consultation with the investigator(s) or designee. The DLRT members are responsible for dosing decisions, which may include escalation to the next nominal or intermediate dose, de-escalation to a lower nominal or intermediate dose frequencies, continuation, delay or termination of dosing; or repetition or expansion of a cohort; or determination of RP2D.

See Section 3.1 for more details regarding the study design and the dose escalation plan for this study.

The DLT-observation period is defined as, at minimum, 28 days after the initial dose of AMG 397. Once lead-in dosing period is initiated, the DLT-observation

period is defined as the amount of time for subject(s) for each dose cohort to receive at least 1 week of lead-in dose and 3 weeks of target dose.

A subject is deemed A subject is classified as DLT-evaluable if during the DLTobservation period, the subject: if

- he/she experiences a DLT (and follow up is sufficient to determine the incidence of DLT), or if he/she otherwise Rreceivesd at least 785% of the planned dose of AMG 397 in the DLT window.
- The DLT window is defined as 21 days after the initial dose of AMG 397.Experienced a DLT

Available study data, including data collected after the initial DLT windowDLTobservation period along with demographics, IP administration, medical history, concomitant medications, adverse events (AE), ECG, vital signs, laboratory results and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

Dose escalation/de-escalation decisions will be guided by the BLRM model of dose toxicity described by **Appendix D**Appendix D. An Amgen representative will notify the sites in writing the dosing decision from the DLRM and when a cohort is open to screen new subjects.

DLTs experienced by subjects after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity.

Dose escalation for each group will continue until any of the following events occur:

- The highest planned dose level is determined to be safe and tolerable (minimum of 6 evaluable subjects)
- MTDs are identified for each group where BLRM repeats the recommendation of a dose level (minimum of 6 evaluable subjects)
- The maximum of 30 evaluable subjects have been enrolled in each group. If fewer than 6 subjects are treated at the MTD/RP2D, additional subjects may be enrolled to confirm safety and tolerability.

If there are concerns about the tolerability of the current continuous dosing schedule, alternative dosing schedules or lower dose(s) may be explored, including modification of the lead-in period dosing regimen. The alternative dose and schedule will be jointly determined by the investigators and the Amgen medical monitor, based on pharmacokinetic and safety and toxicity data.



# 21. Section 6.2.1.3, Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Removed strikethrough text, Added text in BOLD

# NOTE: For subjects who meet clinical or laboratory TLS per Cairo-Bishop criteria (Appendix K and L) see Section 6.2.1.1.1 for dose adjustment details.

#### Dosage Adjustments

The subject should continue on the same dose of AMG 397 throughout the study unless

the following events occur:

- For subjects experiencing an adverse event meeting the DLT definition or intolerable related adverse events BUT showing evidence of response, there will be an option to reduce the dose to the immediate next lower dose level shown to be safe and tolerable in the dose escalation part of the study.
- AMG 397 can be resumed once the adverse events recover to baseline or Grade 1 and the reintroduction of AMG 397 is deemed safe by the Investigator, Amgen's Medical Monitor, and Global Safety Officer.

**NOTE:** Subjects must be informed of the risk of continuing on therapy. Each subject is only allowed a single dose reduction.

Subjects should not be re-challenged with AMG 397 if the following AMG 397-related adverse events occur:

- Any life-threatening adverse events
- DILI (Drug Induced Liver Injury) meeting Hy's law
- Persistent grade 3 adverse events that do not recover to baseline or Grade 1 within 4 weeks of last dose
- Any treatment-related adverse event meeting DLT-criteria that recurs

#### Dosage Delays

The investigator should inform the Amgen Clinical team as soon as the unexpected dosage delay occurs. The following dosage delay rules apply:

During the DLT window, if the dosing is delayed for more than 48 hours the subject will be removed from the study and will be replaced.

After DLT window:

- If the dosing delay is ≤ 3 weeks, the subject should resume the treatment as soon as possible if deemed safe by the investigator.
- If the dosing delay is more than 4 weeks (missing 1 cycle):
  - Due to treatment related AEs, the subject will be removed from the study.
  - Due to other conditions other than treatment related AEs, the case will be reviewed by Amgen medical monitor to determine whether the subject will be allowed to resume AMG 397 treatment.



#### Rules for Dose Withholding

AMG 397 should be withheld for any of the following:

- Suspected DLT (including AEs that meet DLT definition outside <u>DLT windowDLT-observation period</u>)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 x ULN or total bilirubin greater than 1.5 x ULN

#### Rules for Restarting

AMG 397 dosing can be resumed:

- If the toxicities resolve to grade ≤ 1 or return to subjects' baseline values
- Restarting of therapy is deemed safe by the investigators and Amgen's medical monitor.

#### Rules for Permanent Discontinuation

Subjects will permanently discontinue from the investigational product if:

- Subjects experience adverse events meeting the DLT criteria at any time. Subjects
  will be followed until the DLT is resolved, returns to baseline value or is considered
  stable. Subjects will be withdrawn from AMG 397 treatment and will be treated as
  deemed appropriate by the investigator or treating physician. Except for:
  - Subjects showing evidence of response or subjects who in the opinion of the investigator may be responding to AMG 397, may have the option to continue therapy once the adverse events recover to baseline or Grade 1 and the re-introduction of AMG 397 is deemed safe by the investigator, Amgen's medical monitor, and Global Safety Officer. The subject should restart at a reduced dose.
  - Subjects who experience TLS as detail, see Section 6.2.1.1.1 for dosing details.
- Intolerability of the study treatment
- The dosing is delayed > 4 weeks due to AMG 397-related adverse events
- Disease progression according to IMWG (MM), Lugano classification (NHL), or 2017 ELN response criteria (AML) and/or per institutional guidelines as applicable
- Clinical significant deterioration of health status
- Withdrawal of informed consent
- Subject becomes pregnant or is breastfeeding
- Initiation of new systemic anti-cancer therapy not provided in this study
- Study is terminated by the sponsor.

CONFIDENTIAL

#### 22. Section 6.3.1; Pre-dosing requirements for AMG 397

#### Added text in **BOLD**

#### 6.3 Other Protocol Required Therapies

6.3.1 Pre-dosing requirements for AMG 397

To mitigate risk of TLS, all subjects are to receive TLS prophylaxis prior to first dose of AMG 397 and prior to any dose escalation. Refer to Section 6.5.7 for specific requirements.

#### 23. Section 6.4; Dose Limiting Toxicities

#### Removed strikethrough text, Added text in BOLD

#### 6.36.4 Dose Limiting Toxicities

The grading of adverse events will be based on the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (available online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Determination of the severity of adverse events will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The relationship of an adverse event to investigational product will be determined by the Investigator. An event should be considered related to treatment if, in the Investigator's medical judgment, there is a reasonable possibility that the event may have been caused by AMG 397.

#### For MM and NHL subjects only:

A DLT is defined as a clinically significant, treatment-related AE(s), with certain exceptions, below that occur during the DLT windowDLT-observation period (day 1 through day 21 after the administration of the first dose of AMG-397see Section 6.2.1.2) including any-that is:

- ≥ Grade 3 non-hematological AE's EXCEPT:
  - o ≥ Grade 3 fatigue if <7 days
  - Grade 3 nausea, vomiting and/or diarrhea if < 3 days and controlled with medical management
  - Laboratory parameters of grade ≥ 3 that improve with medical management to grade ≤ 2 within 3 days
- ≥ Grade 4 hematologic AE's AND:
  - ≥ Grade 3 neutropenia with fever
  - o ≥ Grade 3 thrombocytopenia with Grade ≥ 2 hemorrhage
  - o ≥ Grade 3 anemia with symptoms requiring intervention (eg, transfusion)

NOTE: ≥ Grade 4 neutropenia must be lasting > 7 days

Any grade 5 AE that is not clearly due to disease progression

≥ Grade 3 non hematological AE



≥ Grade 4 or higher hematologic AE

DLT toxicities do not include fatigue, nausea, diarrhea, vomiting, acute kidney injury, neutropenia, anemia, thrombocytopenia, and lymphopenia unless the following criteria are met:

Hematological toxicity:

- ≥ Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 neutropenia with fever > 38.5°C
- ≥ Grade 3 thrombocytopenia with ≥ Grade 2 hemorrhage
- ≥ Grade 4 thrombocytopenia lasting > 7 days
- ≥ Grade 3 anemia with symptoms or required intervention (eg, transfusion)
- ≥ Grade 4 anemia

Non-hematological toxicity:

- ≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support
- ≥ Grade 3 fatigue persisting > 7 days
- Erade 3 acute kidney injury (creatinine >3 X baseline or > 4.03 mg/dL) lasting > 3 days

#### For AML subjects only:

Due to the nature of AML, hematologic adverse events will not be considered DLTs. However, prolonged pancytopenia in the presence of a hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) that lasts longer than 42 days will be considered dose-limiting myelosuppression.

#### Non-hematological toxicity:

- ≥ Grade 3 nausea, vomiting or diarrhea persisting more than 3 days despite optimal medical support
- ≥ Grade 3 fatigue persisting > 7 days
- Any other ≥ Grade 3 adverse event
- Failure to recover from AMG 397 related toxicities to grade ≤ 1 or baseline severity after delaying next cycle up to 14 days

#### For all subjects: Tumor Lysis Syndrome:

Any Clinical TLS -(refer to Appendix KJ)

## If a DLT of TLS is observed during the lead-in period, it will be attributed to the

lead-in

period and a modification may be made to the lead-in period regimen for subsequent



cohorts. Any other DLTs observed during the lead-in and/or designated cohort dosing

period may require a modification of the designated cohort dose (and/or lead-in period

regimen, if appropriate) as directed per the Dose Escalation Guidelines.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin level (TBL) of > 2x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 6.66.7 for hepatotoxicity management and **Appendix A** for further explanation of Hy's law case and Management of Hepatic Function). Grade 3 or 4 elevation of serum lipase without clinical signs or symptoms of pancreatitis.

#### 24. Section 6.5.7; Tumor Lysis Syndrome (TLS)

#### Added below text

#### Prophylaxis and Management of TLS

Tumor lysis syndrome prophylaxis must be initiated in all subjects prior to the first dose of AMG 397 and prior to every dose escalation.

The management recommendations below focus on the minimum initial responses

required. If a diagnosis of TLS is established, ongoing intensive monitoring and

multi-disciplinary management will be conducted per institutional protocols

(Coiffier et al, 2008; Cairo et al, 2004).

- Initiate allopurinol or equivalent to reduce uric acid level. This should be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks. Other agents to reduce uric acid level, such as rasburicase may be used per PI discretion. Dosing per institutional guidelines.
- All subjects will be hospitalized for intensive monitoring:
  - For the first 2 doses received, beginning 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
  - Once lead-in dosing is initiated (see Section 6.2.1.1.1):
    - For the first 2 doses received (Lead-in dosing), beginning at least 24 hours prior to first dosing day (Day -1) until 24 hours post the second dose
    - Each time an additional week of lead-in dosing is instituted (Section 6.2.1.1.1)
    - For the first 2 doses received after the dose is escalated (target dose) beginning at least 24 hours prior to dosing day (usually day 7) until 24 hours post the second dose
- During hospitalization, intensive safety laboratory monitoring per designated timepoints per Table 4 and/or 5 to identify and prompt management of any metabolic changes.
  - Pre-treatment serum chemistry and hematology laboratory samples must be drawn within 24 hours prior to first dose, and electrolyte values (ie, potassium, uric acid, inorganic phosphorus, calcium) must be reviewed and within normal range prior to AMG 397 dosing. The investigator's decision to proceed with AMG 397 treatment initiation may be based on these laboratory values. These labs must be reviewed in real time by the investigator.

**NOTE:** If the potassium, uric acid, inorganic phosphate and/or creatinine values are higher than the normal range or the calcium is lower or higher than the normal range, dosing can be resumed following review of laboratory values and agreement between the Amgen medical monitor and investigator.



- Prophylactic reductions of potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended per PI discretion.
- Day 2 dosing of AMG 397 should not be administered until the 24 hours post-dose laboratory values are reviewed by the investigator.
- All 24 hour laboratory assessments may be taken ± 2 hours, if necessary.
- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria (Appendix L) are met, no additional AMG 397 doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Upon admission, IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs and as needed per Investigator discretion.
- Monitor for signs and symptoms of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared.
- Management recommendations of laboratory abnormalities as stated below:

Abnormality	Management Recommendations <sup>1,2</sup>
Hyperkalemia (including rapidly ris	-
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	<ul> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still &lt; upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour.</li> <li>Resume per protocol testing if change in potassium is &lt; 0.2 mmol/L, and potassium &lt; ULN, and no other evidence of tumor lysis.</li> </ul>
	<ul> <li>At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.</li> </ul>
Potassium > upper limit of normal	<ul> <li>Perform STAT ECG and commence telemetry.</li> <li>Nephrology notification with consideration of initiating dialysis.</li> <li>Administer Kayexalate 60 g (or Resonium A 60 g).</li> <li>Administer furosemide 20 mg IV × 1.</li> </ul>
	<ul> <li>Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and</li> </ul>
	<ul> <li>creatinine in 1 hour STAT.</li> <li>If potassium &lt; ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.</li> </ul>

Abnormality	Management Recommendations <sup>1,2</sup>
Hyperkalemia (including rapidly ris	sing potassium) (continued)
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	<ul> <li>Perform STAT ECG and commence telemetry.</li> <li>Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis.</li> <li>Administer Kayexalate 60 g (or Resonium A 60 g).</li> <li>Administer furosemide 20 mg IV × 1.</li> <li>Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV.</li> <li>Administer sodium bicarbonate 1 to 2 mEq/kg IV push.</li> <li>If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. <u>Do not administer in same IV line as sodium bicarbonate</u>.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.</li> </ul>
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	<ul> <li>Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes).</li> <li>If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> </ul>
Uric acid $\geq$ 10 mg/dL (595 µmol/L) Uric acid $\geq$ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase $\geq$ 0.3 mg/dL ( $\geq$ 0.027 mmol/L) from pre-dose level	<ul> <li>Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes).</li> <li>When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.</li> <li>Consult nephrology (or other acute dialysis service).</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If uric acid &lt; 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> </ul>



Abnormality	Management Recommendations <sup>1,2</sup>
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) <u>AND</u> Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	<ul> <li>Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring.</li> <li>Telemetry.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> <li>Calculate corrected calcium and check ionized calcium if albumin low.</li> </ul>
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	<ul> <li>Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).</li> <li>Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL).</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.</li> <li>If phosphorus &lt; 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.</li> </ul>
Creatinine	
Increase $\geq 25\%$ from baseline	<ul> <li>Start or increase rate of IV fluids.</li> <li>Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.</li> </ul>

#### **References:**

1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.



#### 25. Section 6.8; Concomitant Therapy

#### Added text in BOLD:

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, G-CSF and other care as deemed appropriate, and in accordance with their institutional guidelines. For subjects with AML hydroxyurea for 7 days at a dose of 1 - 10 g/day is allowed prior to the first cycle of AMG 397 treatment for subjects with high WBC (> 25,000 cells/ul) and during the first cycle but not on dosing days at a dose of up to 5 g/day.

#### 26. Section 6.10; Excluded Treatments and Procedures During Study Period

#### Removed strikethrough text, Added text in BOLD

#### 6.96.10 Excluded Treatments and Procedures During Study Period

The following medications and/or therapies should not be administered within the timeframes specified prior to enrollment or during the study (unless otherwise specified):

- Allogeneic stem cell transplant within 6 months of study day 1
- Autologous stem cell transplant < 90 days prior to study day 1</li>
- Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, retinoid therapy, or investigational agent or procedures)
- within 14 days of study day 1.
- Prior-sSystemic radiation therapy must have been completed at least 28 days before study day 1. Prior-or focal radiotherapy-completed at 14 days before study day 1.
- Over-the-counter or prescription medication(s) -within 14 days or 5 half lives (whichever is longer), prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor
- Use of aAny known inhibitors of P-gp within 14 days or 5 half lives (whichever is longer) or grapefruit juice or grapefruit containing products within 7 days prior to study day 1 that wereas not reviewed and approved by the principal investigator and the Amgen medical monitor
- Use of hHerbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to study day 1 that wereas not reviewed and approved by the principal investigator and the Amgen medical monitor
- Use of Any known cytochrome P450 (CYP) 3A4 sensitive substrates, with a narrow therapeutic window, within 14 days or 5 half lives (whichever is longer) of the drug or its major active metabolite prior to study day 1 that waweres not reviewed and approved by the principal investigator and the Amgen medical monitor

If use of any **other** prior or concomitant medication or procedure is in question, please refer to prescribing information and/or consult with Amgen Medical Team.



#### 27. Section 7.1, Schedule of Assessments

Removed strikethrough text, Added text in BOLD

#### 7.1 Schedule of Assessments

Please refer to Table 4 for Schedule of Assessments.

Once lead-in dosing is initiated follow Table 5 for Cycle 1 only. For all subsequent cycles and study periods follow Table 4.

	SC															TRI	EATI	MEN	Т															
CYCLE(S)	SCREENING														1														2		Every cy from 3 beyon	S.	SAF	
WEEK(S)	ING											1											2			3		1	2	3	1			HE
DAY(S)	- 21 to -2	-1					1								2				3	4			8			15	22	1	8	15	1 45	EOT	SAFETY FOLLOW-UP	LTFU (246)
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	after D2	48h after D2 dose	Pre	0	2	3	5		Pre-	dose	unles	ss sp	ecified			
Informed consent	х																																	
Clinical evaluation (1)	х	x	х																x	x	х					х	х	х	х	х	х	x	X	
Vital signs (T, BP, HR, RR)	х	x	х				x	х	х	х	х				х	х	х	х	х	х	х					х	х	х	х	х	х	x	х	$\square$
12-lead ECG (2)	х	х	X (2)		х	х	х	х	х	Х	х		х	х	х	х	х	x	х	х	Х		х	х	Х	х	х	х	х	х	х	х	x	
Echocardiogram or MUGA	х																															х		
Hospitalization (3)			•	-		_										-	-	•																
TLS prophylaxis (4)		x																																
AMG 397 Dosing (5)				x								x										x				for 5 d	2 cor lays l	nsecu break	tive o at a v	days 1 weekl	once dai followed ly interva ment cyc	by		
Dosing diary review (524)											х								x		х					х	Х	х	х	1	X	X		
AE Reporting					•	-														-	-						_							-
SAE Reporting		-		-													_												_	_			_	→
Prior /concomitant medication(s)	•																																	•
Survival/Subsequent anti-cancer therapy (621)																																		x



	S															TR	EAT	MEN	π															
CYCLE(S)	SCREENING														1														2		Every cycle from 3 & beyond		SAF	
WEEK(S)	NG											1											2			3		1	2	3	1			LTFU
DAY(S)	- 21 to -2	-1					1								2				3	4			8			15	22	1	8	15	1 46	EOT	SAFETY FOLLOW-UP	LTFU (246)
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	12	Pre- dos	0	1	2	3	5	8	12	24h after D2 dose	48h after D2 dose	Fie	0	2	3	5		Pre-	dose	unle	ss sp	ecified			
													L	АВ	AS	SES	SM	ENT	rs															
AMG 397 PK (73)			х		х	х	х	х	х	х	х		х	х	х	х	х	х	х	х	х		х	х	х							х		
CBC with diff (48)	х	x	х				×	×	x	×	х				×	×	×	×	х	x	х					х	х	х	х	х	х	х	х	
Chemistry (94)	х	x	х				x		x	x	x				x	x	x	x	x	x	х					х	х	х	х	х	х	х	х	
Coagulation (4)	х	x	х								x								x	x	х					х	х	х	x	х	х	х	x	$\square$
Pregnancy test (510)	х		х																									x			x	х		$\square$
Urine sample collection (11)	x		x						x		x						x				x				x			x			x			$\square$
Hepatitis serology, HIV	х																																	
										BI	OM	AR	(ER	an	d D	ISE	ASE	AS	SE	SSN	IEN	TS				_								
Bone marrow aspirate (127)	х																																	$\square$
Whole blood Na/Hep (813)			х				x	х			х					×			×	×														
Whole blood Cytochex-(Dose escalation only) (914)			х								x								x	x	x					×								
Plasma	х																																	
Serum	х																																	

	s															TR	EAT	MEN	п															
CYCLE(\$)	SCREENING														1														2		Every cycli from 3 & beyond		SAF	
WEEK(S)	ING											1											2			3		1	2	3	1			LTFU
DAY(S)	- 21 to -2	-1					1								2				3	4			8			15	22	1	8	15	1 46	EOT	SAFETY FOLLOW-UP	LTFU (2 <del>48</del> )
HOUR(S) (relative to time of dosing)			Predose		1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8	12	after D2	48h after D2 dose	Pre	0	2	3	5		Pre-	dose	unle	ss spi	ecified		q	
Cell Pellet	х																																	
MM SUBJECTS	DNL	Y.		_																								_						
SPEP/UPEP/ Immunofixation (4015)	х																											x			х	х		
SFLC (416)	х																											х			х	х		
Beta-2 microglobulin	х																															х		
Quantitative Ig (127)	х																															х		
Bone marrow biopsy	х																																	
Bone marrow aspirate (18)			-				-									- Rep	eat o	ollec	tion i	n cas	e of C	:R												
Plasmacytoma (149)	х																																	
Skeletal survey (2045)	х																																	
NHL SUBJECTS	ON	LY			_																						_							
Lymph Node Biopsy	х																																	
Whole blood plasma (Dose expansion only) (2146)	x																											х			X ( <b>4621</b> )	х		
Bone marrow biopsy (2247)	х																																	

Approved

#### 28. Section 7.1, Schedule of Assessments

#### Added Table 5

#### Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

CYCLE																					C	CLE	10	NLY																	
DAY(S)	- 21 to -2	-1					1							2					3	4	7					8							1	9				10	11	15	22
HOUR(S) (relative to time of dosing)			Pre- dose	0	1	2	3	5	8	12	Pre- dose	0	1	2	3	5	8		24h after D2 dose	afte D2	r	Pre- dose	0	1	2	3	5	8	12	Pre- dose	. 0	1	2	3	5	8	12	24h after D9 dose	D9	1	
Informed consent	х																																								
Clinical evaluation (1)	х	х	х								х								Х	х	х	х								х								х	х	х	х
Vital signs (T, BP, HR, RR)	х	х	х				х	х	х	х	х				х	х	х	х	Х	х	х					х	х	х	х	х				х	х	х	х	х	х	х	х
12-lead ECG (2)	х	х	X (2)		х	х	х	х	х	х	х		х	х	х	х	х	х	Х	х	x			х	х	х	х	х	х	х		х	х	х	х	х	х	х	х	х	Х
Echocardiogram or MUGA	х																																								
Hospitalization (3)		•															-					<												•			•				
TLS prophylaxis (4)		Х																			Х																				
AMG 397 dosing (5)				х								х											Х								Х								)	(5)	
Dosing diary review (5)											х										х															1		х		х	х
AE Reporting							<																															•			
SAE Reporting			-		•																																	→			
Prior /concomitant medication(s)		•																																				→			

Footnotes are defined on page 64

Page 37 of 56

Page 1 of 4



Product: AMG 397 Protocol Number: 20170173 Date: 28 March 2018

|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | СҮ                                                                                                                                                                                                                                                                                                                                                                                                               | CLE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1 01                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | ILY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-----|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| -<br>21<br>to<br>-2 | -1                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 7                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                | !  | 9  |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              | 10                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 15                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                     |                                                                 | Pre<br>dos                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | e- 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Pre-<br>dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | after<br>D2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | after<br>D2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  | Pre-<br>dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 5  | 8   | 12      | Pre-<br>dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  
                                                                                                                                                                                                                                                | 2  | 3  | 5  | 8                                                                                                                                                                                                            | 12                                                                                                                                                                                                           | after<br>D9                                                                                                                                                                                                                 | after<br>D9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | •                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | •                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | L                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | AB /                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | ASS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | SES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | SN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | IEN <sup>.</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | TS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | •                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | : )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                        | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | х  | х   | х       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  
                                                                                                                                                                                                                                                | х  | х  | х  | х                                                                                                                                                                                                            | х                                                                                                                                                                                                            | х                                                                                                                                                                                                                           | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   | х                                                               | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | х                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              | х                                                                                                                                                                                                                           | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | x                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   | х                                                               | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                          | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | х                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    | х   | х       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    | х  |    | х                                                                                                                                                                                                            | х                                                                                                                                                                                                            | х                                                                                                                                                                                                                           | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   | х                                                               | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | х                                                                                                                                                                                                                                                                                                                                                                                                                | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              | х                                                                                                                                                                                                                           | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| х                   |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    | х   | 1       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    | х                                                                                                                                                                                                            | <u> </u>                                                                                                                                                                                                     |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | BIO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | MA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | RK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | and                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | I DI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | SE/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ASI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | E AS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | SSE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | SS                                                                                                                                                                                                                                                                                                                                                                                                               | ME                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | NT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| x                   |                                                                 | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Т                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Τ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Τ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Γ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | х                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | х  | 1   |         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    | 1  |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     |                                                                 | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              | х                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | х                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | | | |
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| х                   |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |     |         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                |    |    |    |                                                                                                                                                                                                              |                                                                                                                                                                                                              |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                     | to<br>-2<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X<br>X | to     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2     -1       -2 | to        1           -2         -1           -2         Predos           -2         X           -2         X           -2         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X           X         X | to         -1           -2         Pre-<br>dose         0           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X           X         X         X | to       -1         -2       Pre-<br>dose       0       1         X       X       X       X         X       X       X       X       X         X       X       X       X       X         X       X       X       X       I         X       X       X       X       I         X       X       X       X       I         X       X       X       X       I         X       I       X       I       I         X       I       X       I       I         X       I       X       I       I         X       I       I       I       I         X       I       I       I       I       I         X       I       I       I       I       I         X       I       I       I       I       I         X       I       I       I       I       I         X       I       I       I       I       I       I         X       I       I <thi< th="">       I       I       I       &lt;</thi<> | to       -1         2       -1         Pre-<br>dose       0       1         X       X       X       X       X         X       X       X       X       X       X         X       X       X       X       I       I         X       X       X       I       I         X       X       X       I       I         X       X       X       I       I         X       X       X       I       I         X       X       X       I       I         X       I       X       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I         X       I       I       I       I       I         X | to       -1       Pre-dose       0       1       2         Image: Im | to       -1       Pre-<br>dose       0       1       2       3 $2$ $3$ $3$ $3$ $3$ $3$ $3$ $2$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ $3$ < | to       -1         2       -1         Pre-<br>dose       0       1       2       3       5         X       X       X       X       X       X       X       X         X       X       X       X       X       X       X       X       X         X       X       X       X       X       X       X       X       X         X       X       X       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I <thi< th="">       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I<!--</td--><td>to       -1       Pre-<br/>dose       0       1       2       3       5       8         <math>x</math> <math>x</math></td><td>to       -1       Pre-<br/>dose       0       1       2       3       5       8       12         I       I       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X</td><td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td><td>to       -1       Pre-<br/>dose       0       1       2       3       5       8       12       Pre-<br/>dose       0         x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x<td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td><td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I 
     I       I       I       I       I       I       I       I       I       I       I       I       I       I</td><td>to       -1       -1       -1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3         W       Pre-<br/>dose       0       1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3         V       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                             
</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<></td></t<></td></t<></td></t<></td></td></thi<> | to       -1       Pre-<br>dose       0       1       2       3       5       8 $x$ | to       -1       Pre-<br>dose       0       1       2       3       5       8       12         I       I       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X | to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I | to       -1       Pre-<br>dose       0       1       2       3       5       8       12       Pre-<br>dose       0         x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x       x <td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I
      I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td> <td>to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I</td> <td>to       -1       -1       -1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3         W       Pre-<br/>dose       0       1       2       3       5       8       12       Pre-<br/>dose       0       1       2       3         V       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X</td> <td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1   
   -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<></td></t<></td></t<></td></t<></td> | to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I | to       -1       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I      
I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I       I | to       -1       -1       -1       2       3       5       8       12       Pre-<br>dose       0       1       2       3         W       Pre-<br>dose       0       1       2       3       5       8       12       Pre-<br>dose       0       1       2       3         V       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1 <t< td=""><td>to       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                
            </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<></td></t<></td></t<></td></t<> | to       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1       ·1 <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1      
-1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1     
 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<></td></t<></td></t<> | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1 <t< td=""><td>to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2      
3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<></td></t<> | to       -1       -1       -1       -1       -1       -1       2       3       5       8       12       Pre-dose       0       1       2       3       5       8       12       24h         M       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X       X <t< td=""><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12       <math>22^{24h}</math><br/></td><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1
      -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<></td></t<> | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       2       3       5       8       12 $22^{24h}$<br> | 21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1 <td< td=""><td>21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1      
.1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1   
   1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<></td></td<> | 21       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .1       .2       .3       .4       .7       .1       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .4       .7       .1       .1       .2       .3       .5       .8       .12       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2       .2 <t< td=""><td>21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V</td><td>to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1    
  1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td></td></t<> | 21       1       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V       V | to       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1       -1 <t< td=""><td><math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>4</math> <math>7</math> <math>1</math> <math>1</math> <math>2</math> <math>3</math> <math>5</math> <math>8</math> <math>12</math> <math>2^{2h}</math> <math>4^{2h}</math> <math>4^{2h}</math></td><td>21                             </td><td>210                                                                                                              </td><td>21<br/>1                                                                                                              </td><td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td><td>21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3</td><td>21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70</td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>21                                                                                                               </td><td>211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111</td><td>111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111</td></t<> <td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td> <td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       <th1< th=""> <th1< th=""></th1<></th1<></td> <td>1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1</td> | $1$ $1$
$1$ $1$ $1$ $1$ $1$ $1$ $2$ $3$ $4$ $7$ $1$ $1$ $2$ $3$ $5$ $8$ $12$ $2^{2h}$ $4^{2h}$ | 21 | 210 | 21<br>1 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 | 21       1       1       1       1       1       1       1       1       2       3       4       7       2       3       4       7       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       4       7       2       3       5       8       1       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       3       5       8       1       2       2       3       5       8       1       2       2       3       5       8       1       2       2       3       3       4       7       2       3       3       3       3       3       3       3       3       3       3 | 21       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       2       3       4       7       1       2       3       5       8       12       2       4       48       2       10       1       2       3       4       7       1       2       3       5       8       12       2       48       70       1       2       3       5       8       12       2       48       70       70       1       2       3       5       8       12       2       70       70       71       21       3       5       8       12       2       3       4       7       70       1       2       3       5       8       12       2       3       4       7       70       12       3       5       8       12       70       70       70       70       70       70       70       70       70       70       70       70 | 21 | 21 | 21 | 211111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111 | 111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111111 | 111111111111112347123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358120123581201235812012358121111111111111111111111111111111111111111111111111111111111 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 <th1< th=""> <th1< th=""></th1<></th1<> | 1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1       1 |

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined on page 64

Page 2 of 4

Product: AMG 397 Protocol Number: 20170173 Date: 28 March 2018

#### CYCLE CYCLE 1 ONLY -21 11 15 22 DAY(S) -1 1 2 3 4 7 8 9 10 to -2 24h 48h after after 24h 48h HOUR(S) (relative after after D9 D9 Pre-dose 12 Pre-dose 12 Pre-dose 0 Pre-8 0 0 8 2 5 8 12 0 1 2 3 5 1 2 3 5 8 12 1 2 3 5 1 3 to time of dosing) D2 D2 dose dose dose dose dose **BIOMARKER and DISEASE ASSESSMENTS** MM SUBJECTS ONLY SPEP/UPEP/ Х Immunofixation (15) )TOV( Х SFLC (16) Beta-2 Х microglobulin Quantitative Ig (17) Х Bone marrow Х biopsy Х Plasmacytoma (19) Skeletal survey (20) х Page 3 of 4

### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined on page 64



Product: AMG 397 Protocol Number: 20170173 Date: 28 March 2018

#### CYCLE CYCLE 1 ONLY -21 11 15 22 DAY(S) -1 1 2 3 4 7 8 9 10 to -2 24h 48h after after D2 D2 24h 48h Pre-dose 0 HOUR(S) (relative after after D9 D9 Pre-dose Pre-dose 12 Pre-dose 0 3 8 12 2 2 5 8 0 1 2 3 5 0 1 2 5 8 12 1 3 5 8 1 3 12 to time of dosing) dose dose dose dose NHL SUBJECTS ONLY Lymph Node Х Biopsy Whole blood plasma Х DTOV( (Dose expansion only) (21) Bone marrow Х biopsy (22) PET-CT and CECT Х Imaging (23) Х MRI Brain (24) Page 4 of 4

#### Table 5. Schedule of Assessments (Cycle 1 ONLY After Lead-in Dosing is Implemented)

Footnotes are defined on page 64

\_\_\_\_\_

**AMGEN** 

#### 29. Section 7.1, Footnotes for Table 4 and Table 5

Removed strikethrough text, Added text in BOLD

Page 41 of 56

Foo	tnotes for Table 4 and Table 5 <del>Table 4</del>
1	Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight. Medical and surgical history, and height need only be collected at the screening visit.
2	<ul> <li>Three baseline ECGs (pre-dose on day 1) will be collected approximately ≥ 15 minutes apart (+/- 5 minutes), with each baseline ECG in triplicate run consecutively (ie, &lt;30 seconds apart); Total of 9 ECGs]</li> </ul>
	<ul> <li>Triplicate ECGs run consecutively (ie, &lt;30 seconds apart), at time points designated in the schedule of assessments</li> </ul>
3	See Section 6.5.7 for more details regarding hospitalization for TLS prophylaxis
	Hospitalization for the purpose of TLS prophylaxis will not be captured as an SAE.
4	See Section 6.5.7 for more details regarding TLS prophylaxis.
5	See Section 6.2.1.1 for details regarding dosage, administration, and schedule.
	<ul> <li>See Section 6.2.1.1.1 and Table 5 for details regarding dosage, administration, and schedule once lead-in dosing is implemented.</li> </ul>
6	For Dose Expansion subjects only:
	o Collected during LTFU period
73	<ul> <li>For PK collections on Cycle 1, PK samples should be collected within +/- 15 min of the designated time points.</li> </ul>
	<ul> <li>PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as</li> </ul>
	close as possible and record the actual collection time in the eCRF.
	Note: It is important to document the exact date and time of IP administration and PK collection.
84	Refer to Section 7.2.15 7.2.15 for list of SafetyCBC lab tests required.
	Note: Subjects with a Grade 4 neutropenia should have their counts repeated every 24-48 hours until return to baseline and the use of G-CSF should be considered.
9	Refer to Section 7.2.15 for list Chemistry panel lab tests required.
	<ul> <li>See Section 6.5.7 for chemistry lab tests required for TLS prophylaxis and management</li> </ul>
105	Serum pregnancy test performed at screening; urine or serum pregnancy test at all other timepoints for females of childbearing potential.
116	Please collect urine for UA which is done per local lab.
	<ul> <li>Any remaining urine will be sent to the central lab for analysis. Please refer to lab manual for preparation and transport procedures.</li> </ul>
	<ul> <li>On cycle 1, day 1, collect urine sample at least 5 hours post-dose of AMG 397.</li> </ul>
	<ul> <li>After cycle 1, urine sample may be collected at the following designated timepoints.</li> </ul>
127	
	hybridization (FISH) and other biomarker assays.
8	<ul> <li>Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on days 1 and 2, and 24 hours after day</li> </ul>
	2 1 during week 1. In th second week of Cycle 1, samples will be collected pre dose on day 8, 3 and 5 hours post dose on day 8, and 24 hours often dow 8
	after day 8. A CBC with differential will be tested locally with each whole blood biomarker during cycle 1. (See Footnote 4)
13	
13	<ul> <li>Biomarker NaHep whole blood samples will be collected pre-dose on Cycle 1 day 1, 3 and 5 hours post dose on day 1, and 24 hours after day 1 during week 1 as indicated in Table 4.</li> </ul>
	<ul> <li>Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follows: In th second week of Cycle 1,</li> </ul>



Foo	otnotes for Table 4 and Table 5 Table 4
149	For Dose escalation subjects only: Biomarker Cytochex whole blood samples will be collected pre-dose on days 1, pre-dose day 2, 3, 4, 8, 9, 10, and 1524 hours after day 2, and pre-dose day 8, in the first treatment cycle. Biomarker Cytochex whole blood samples will be collected pre-dose on day
	1, 2, 3, 4, and 8 as indicated in Table 4.
	<ul> <li>Upon commencement of Lead-In dosing, additional samples will be collected indicated in Table 5 as follow: pre-dose on days 9, 10, and 15.</li> </ul>
For	r MM subjects only [10-15-20]:
50	<ul> <li>Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP) is required for all subjects at screening.</li> </ul>
	<ul> <li>Thereafter, SPEP is to be done at each time point for all patients as indicated in the schedule of assessment.</li> </ul>
	<ul> <li>UPEP with 24-hour urine collection is required at each time point only if screening UPEP shows measurable paraprotein in the urine. If screening UPEP in negative, spot urine is required at each time point.</li> </ul>
	<ul> <li>If positive for paraprotein, a 24-hour urine collection with UPEP must be done at the next assessment and at each subsequent assessment unless the UPEP shows an absence of paraprotein. Immunofixation is required at next assessment only if SPEP or UPEP results are zero/undetectable.</li> </ul>
	<ul> <li>See lab manual for collection and shipment details.</li> </ul>
164	Serum free light chain (SFLC) assay and ratio will be performed at each marked time point.
72	Quantitative Immunoglobulin (Total IgG, IgA, IgM) obtained at screening and will be repeated only if clinically indicated (ie; frequent infection despite multiple myeloma disease control).



Foo	tnotes for Table 4 and Table 5
183	Additional bone marrow samples are to be collected to confirm CRs as well as for MRD biomarker analysis. Additional samples may be obtained every six months after CR and/or at time of relapse.
194	Plamacytoma survey
	<ul> <li>For subjects without a history of extramedullary disease, assessment by physical examination at screening is acceptable.</li> </ul>
	<ul> <li>Plasmacytoma evaluation is to be repeated during treatment only to confirm a response of PR or better, to confirm PD, or if clinically indicated. If clinically indicated due to history of extramedullary disease, the same technique (may include ultrasound, x-ray, CT scan, MRI, PET, or other standard-of-care method) must be employed for each measurement.</li> </ul>
204 5	Skeletal survey to be repeated Q8W if clinically indicated ie; new symptoms (bone pain) arises, consider obtaining MRI for subjects with bone pain but skeletal survey is normal.
NHL	(DLBCL for dose expansion) subjects only [2116-2418]:
214	For dose expansion subjects only:
6	<ul> <li>Whole blood plasma may be obtained pre-dose on day 1 of Cycle 2, and every 8 weeks thereafter, and EOT. Samples must be collected, processed, and frozen within 4 hours of phlebotomy and per the laboratory manual.</li> </ul>
	<ul> <li>Additional whole blood plasma samples are obtained at time of relapse.</li> </ul>
224 7	Bone marrow evaluation (core biopsy with or without aspirate) may be performed if there has been previous histologic evidence of bone marrow involvement. An optional tumor biopsy may be collected at time of relapse per institutional guidelines at PI discretion.
234 8	PET/-CT and CECT Imaging with time points at screening, Cycle 2, every 8 weeks thereafter, and EOT. If not acquired on the same day, every effort should be made to complete PET-CT and CECT within 3 days of each other.
24	For Both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI/CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.
254	For AML Subjects only [2519]:
9	<ul> <li>Bone marrow samples must be obtained at pre-dose on day 1 of Cycle 2, every 8 weeks thereafter, and EOT.</li> </ul>
	<ul> <li>Additional bone marrow sampling may occur at other time points at the PI's discretion as clinically indicated throughout course of treatment</li> </ul>
260	For Dose Expansion subjects only:
	Long-term follow up (LTFU) will be conducted every 3 months from the last visit for up to 1 year from the first dose of AMG 397 for all subjects who have not withdrawn consent by telephone or chart review to assess for survival, disease progression and/or the commencement of subsequent cancer therapy only.



#### 30. Section 7.2.8, Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

#### Removed strikethrough text, Added text in BOLD

#### 7.1.87.2.8 Echocardiogram (ECHO) / Multigated Acquisition (MUGA) Scan

ECHO or MUGA will be performed to assess cardiac ejection fraction and cardiac valve abnormalities and will be performed at time points specified in the Schedule of Assessments (see Section 7.1). Additional ECHO/MUGAA, cardiac -assessments imaging and cardiac assessments are to be conducted if any clinical signs or symptoms of cardiomyopathy or other cardiac compromise are noted.

#### 31. Section 7.2.9 Dosing Diary Review

#### Added text in **BOLD**

#### 7.2.9 Dosing Diary Review

A dosing diary will be provided for subjects to record the date, time, and number of tablets consumed each dose. The dosing diary is to be brought to each study visit and reviewed by study staff (see Section 7.1).

The dates of any missed doses or instances of emesis associated with tablet administration will asked to be recorded in the subject drug diary.

#### 32. Section 7.2.11.1 Imaging and Disease assessments, 2<sup>nd</sup> paragraph

#### Added text in **BOLD**

PET-CT and CECT scans required in this protocol will be performed according to the Imaging Manual provided by the central vendor. However, depending on scanner types and availability, as well as local regulations, institutional guidelines may be followed upon consultation with, and approval by, the central vendor. Combined PET-CT whole body scans will be acquired from base of skull to mid-thigh, with the CT portion of the scan used only for attenuation correction. CECT anatomical coverage includes the chest, abdomen, and pelvis (and neck, if not visualized with chest), and the acquisition of separate CECT scans is strongly recommended for staging evaluation. Refer to the Imaging Manual for complete details about PET-CT and CECT scanning procedures and instructions.

PET-CT images should be converted to standardized uptake values (SUV) maps to support comparison across timepoints and to standardize viewing conditions.



If PET-CT and CECT are acquired on the same day, it is strongly recommended that PET-CT is performed prior to CECT. If acquired separately, every attempt should be made to complete PET-CT and CECT within 3 days of each other.

Refer to the Imaging Manual for additional details. Findings will be recorded per eCRF guidelines.

#### 33. Section 7.2.11.2 MRI Brain

Removed strikethrough text, Added text in BOLD

7.2.11.2 MRI Brain

For both Part 1 (dose escalation) and Part 2 (dose expansion), all NHL subjects must have MRI or /CT of the brain performed within 21 days prior to enrollment. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.

#### 34. Section 7.2.14 Blood Samples, Tables 6, 7, and 8

Removed strikethrough text, Added text in BOLD

		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collection	Approximate Number of Collection	Approximate Total Volume (mL)	Approximat e Number of Collection	Approximat e Total Volume (mL)
CBC with diff	<del>54</del>	18	7290	21	84
Laboratory safety (Chemistry Pregnancy test (childbearing females only); coagulation)	8.5 <del>10</del>	25 <del>14</del>	<b>212.5</b> <del>140</del>	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Quantitative Immunoglobulin	10	2	20	2	20
Serum pregnancy test (female of child bearing potential only)	3	5	<del>15</del>		
Blood samples for biomarkers	5	<del>12169</del>	<del>60 <b>4580</b></del>	16	80
Blood samples for PK	5	20	100	32	160
Beta-2 microglobulin, SPEP and SFLC	10	7	70	7	70
Total approximate blood v	olume		52000		762.5

#### Table 65. Approximate Blood Volumes Collected for MM Subjects Only



		No Lead-In Dosing		With Lead-In Dosing	
Test	Volume (mL) per Collectio n	Approximat e Number of Collection	Approximat e Total Volume (mL)	Approximat e Number of Collection	Approximat e Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry <ul> <li>Pregnancy test         <ul> <li>(childbearing females only)</li> </ul> </li> </ul>	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume for escalation		dose	488.5		<u>672.5</u>
Whole blood plasma (Dose expansion subjects only)	5	5	25	5	25
Total approximate blood expansion	l volume for	dose	<u>513.5</u>		<u>697.5</u>

Table 67. Ap	proximate Blood	Volumes Col	lected for NHL	Subjects Only
--------------	-----------------	-------------	----------------	---------------

#### Table 78. Approximate Blood Volumes Collected for AML Subjects Only

		No Lead-	In Dosing	With Lead	-In Dosing
Test	Volume (mL) per Collectio n	Approximat e Number of Collection	Approximat e Total Volume (mL)	Approximat e Number of Collection	Approximat e Total Volume (mL)
CBC with diff	4	18	72	21	84
Chemistry <ul> <li>Pregnancy test         <ul> <li>(childbearing females only)</li> </ul> </li> </ul>	8.5	25	212.5	33	280.5
Coagulation	3	18	54	21	63
Serology (HIV, Hepatitis panel)	5	1	5	1	5
Blood samples for biomarkers	5	9	45	16	80
Blood samples for PK	5	20	100	32	160
Total approximate blood volume			<u>488.5</u>		<u>672.5</u>

#### 35. Section 7.3.1 Blood Samples , Tables 6, 7, and 8

#### Removed strikethrough text, Added text in BOLD

#### 7.2.17.3.1 Blood Samples

Whole blood samples are to be collected for biomarker measurement at several time points as listed in the schedule of assessments. The first set of samples will be collected foron Cycle 1 pre dose on Days 1 and 2, 5 hours post dose on Days 1 and 2, as well as Day 3, 24 hours after the second dose. This set of samples will be collected in 2 tubes at each time point and undergo 2 separate tests: 1) CBC with differential to monitor cell counts (tested locally); 2) Flow cytometric analysis to measure the increase in BAX and Caspase 3 activity in circulating monocytes (MM, NHL) or peripheral blasts (AML) following treatment with AMG 397.

Initially, these blood samples will be collected on Cycle 1 pre-dose on day 1, 3 and 5 hours post-dose on day 1, as well as pre-dose on day 2 according to Table 4. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on Days 1 and 2, 3 and 5 hours post-dose on Day 1, as well as pre-dose on Days 8 and 9, 3 and 5 hours post-dose on Day 8.

In AML subjects, these whole blood samples may also be used to measure pro-survival family members (such as MCL1, BCL2, and BCL2L1 expression) in peripheral leukemic blasts. In Part 1, a second set of whole blood samples will be collected during Cycle 1 on day 1 and 2 pre dose, day 3, day 4, and day 8 pre dose. These A second set of biomarker blood collections will be used to monitor cell counts of immune cell subsets, including T cells, B cells, NK cells, monocytes, and Myeloid Derived Suppressor Cells (MDSCs) following treatment with AMG 397. Initially, these samples will be collected on Cycle 1 pre-dose on days 1, 2, 3, 4, and 8 according to Table 4 above. If Lead-in dosing is initiated due to TLS symptoms, additional samples will be collected for remaining subjects according to Table 5 as follows: Cycle 1 pre-dose on days 1, 2, 3, 4, 8, 9, 10, and 15.

For **DLBCL-NHL** subjects in Part 2 during dose expansion, additional whole blood samples may be taken to assess clinical responses through depth of minimal residual disease status as indicated in schedule of assessments.

#### 36. Section 7.4.1 Screening

#### Added text in **BOLD**

- · Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- · Imaging Assessments, as applicable
- ECG
- ECHO/MUGA
- For NHL subjects, MRI brain (See Section 7.2.11.2)
- · Serious Adverse Event reporting
- · Documentation of concomitant and rescue medications

Subjects may be rescreened at the discretion of the investigator after consultation with the Amgen Medical Monitor. Refer to Section 5 for instructions on rescreening and enrolling subjects.

#### 37. Section 7.4.2 Treatment

#### Removed strikethrough text, Added text in BOLD

#### 7.3.27.4.2 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Section 7.1). Administration of AMG 397 is to be administered as applicable during each visit that it is required.

Treatment visits to include the following:

- Hospitalization (See Section 6.5.7)
- TLS prophylaxis (See Section 6.5.7)
- Clinical evaluations will be collected pre-dose on dosing days and include: physical exam, ECOG status, and weight.
- AMG 397 dosing
- Dosing diary review
- PK (including intensive PK assessments)
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- · Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- · Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- Documentation of concomitant medications

AMGEN

#### CONFIDENTIAL

#### 38. Section 7.4.3 End of Treatment Visit

#### Removed strikethrough text, Added text in BOLD

#### 7.3.37.4.3 End of Treatment Visit

The end of treatment (EOT) visit will occur after the last dose of AMG 397. The end of treatment (EOT) visit will occur upon the decision to end the treatment, disease progression, intolerable adverse event, documented clinical progression or consent withdrawal.

For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Serious adverse events considered related to the investigational product, by the Investigator, or Amgen will be followed until resolved or considered stable.

EOT visits to include the following:

- Clinical evaluations include: physical exam, ECOG status, and weight.
- Dosing diary review
- PK
- ECG
- Vital signs (eg, blood pressure, heart rate, respiratory rate, temperature)
- · Laboratory assessments including local and central laboratories, as applicable
- Pregnancy tests, as applicable
- · Bone marrow aspirate or biopsy as applicable
- Biopsy Assessments, as applicable
- Imaging Assessments, as applicable
- Disease assessments, as applicable
- Serious Adverse Event reporting
- Adverse Event reporting
- · Documentation of concomitant medications



#### **39.** Section 10.4, Adaptive Design, 3<sup>rd</sup> paragraph

#### Removed strikethrough text, Added text in BOLD, Added Table 10 and 11

Operating characteristics for this **BLRM** design are described in **Appendix D**Appendix **D**.

During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher adverse event rate to assess if the threshold for early trial termination has been reached. The stopping rules use a Bayesian approach proposed by Thall, et al (1995) to terminate the study if the posterior probability that the grade 4 or higher adverse event rate is greater than 20% is > 90%. The stopping boundaries assuming a prior distribution of Beta(0.40, 1.60) are presented in Table 10 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 2. Subjects including in a batch may come from different tumor types. The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 11 provide the probability of stopping the study early for given hypothetical true rate of grade 4 or higher adverse events, whereas the stopping criteria in Table 10 are based on situations where the empirical evidence would result in a posterior probability of  $\geq$  90% that the true grade 4 or higher adverse event rate is  $\geq$  20%.

# Table 10. Stopping Boundary for Dose Expansion with Posterior Probability of90% and Grade 4 or Higher Adverse Event Limit of 20%

Number of subjects	Stop study if observing these many grade 4 or higher adverse events
10	≥5
20	≥7
30	Study Complete

True grade 4 or higher adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	0.4%	29.9
0.15	2.7%	29.6
0.20	9.7%	28.7
0.25	22.9%	26.9
0.30	40.8%	24.4

#### Table 11. Operating Characteristics with Batch Size of 10 Subjects



#### 40. Section 13, References

#### Added text in BOLD, Removed strikethrough text

#### 13. REFERENCES

AMG 397 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405.

Ardeshna KM, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. Br J Haematol. 2005;130(3):363-372.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Statistics in medicine. 1998: 17(10):1103-1120

Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. *Nature*. 2010:463:899-905.

Bose P and Grant S. McI-1 as a therapeutic target in acute myelogenous leukemia (AML). Leukemia Research Reports;2013;2(1):12-14.

Boyle MC, Crabbs TA, Wyde ME, et al. Intestinal lymphangiectasis and lipidosis in rats following subchronic exposure to indole-3-carbinol via oral gavage. *Toxicol Pathol.* 2012;40:561-562.

Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 2005;23:1969-78.

Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. J Clin Oncol 2011a;29:487-94.

Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.

Crump M, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496.

Czabotar PE, Lessene G, Strasser A and Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. *Nat Rev Mol Cell Biol.* 2014;15;49-63.

DeVita VT Jr, et al. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet. 1975;1(7901):248-50.

Dimopoulos MA, Richardson PG, Moreau P, Anderson KC. Current treatment landscape for relapsed and/or refractory multiple myeloma. *Nat Rev Clin Oncol.* 2015;12:42-54.

Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD; European LeukemiaNet. Blood. 2010 Jan 21;115(3):453-74.



Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: 2017 ELN recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2017;129(4):424-447.

Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467–73. Erratum in: *Leukemia*. 2006;20(12):2220. *Leukemia*. 2007;21(5):1134.

Durie BG, International Myeloma Foundation. Multiple Myeloma Cancer of the Bone Marrow. Concise Review of the disease and treatment Options. 2011/2012.

Elstrom RL, et al. Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. Clin Lymphoma Myeloma Leuk. 2010;10(3):192-196.

Estey E. Acute myeloid leukemia: 2016 Update on risk-stratification and management. Am J Hematol. 2016 Aug;91(8):824-46.

Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia* 2000;14:476-9.

Estey E, Kornblau S, Pierce S, Kantarjian H, Beran M, Keating M. A stratification system for evaluating and selecting therapies in patients with relapsed or primary refractory acute myelogenous leukemia. *Blood* 1996;88:756

Fisher SG and Fisher RI. The Epidemiology of Non-Hodgkin's Lymphoma. Oncogene. 2004;23(38):6524-534.

Glaser SP, Lee EF, Trounson E, Bouillet P, Wei A, Fairlie WD, et al. "Anti-apoptotic Mcl 1 is essential for the development and sustained growth of acute myeloid leukemia." Genes & Development 2012; 26(2): 120-125.

Haematological Malignancy Research Network.https://www.hmrn.org/statistics/incidence

Hanahan D and Weinberg RA. "Hallmarks of Cancer: The Next Generation." Cell 2011; 144(5): 646-674.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

International Conference on Harmonisation. International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: Nonclinical Evaluation for Anticancer Pharmaceuticals S9, 2009.

Kasper S, Breitenbuecher F, Heidel F, Hoffarth S, Markova B, Schuler M and Fischer T "Targeting MCL-1 sensitizes FLT3-ITD-positive leukemias to cytotoxic therapies" *Blood Cancer J* 2012; 2, e60.

Kaufmann SH, Karp JE, et al. "Elevated Expression of the Apoptotic Regulator McI-1 at the Time of Leukemic Relapse". *Blood* 1998; 91(3)991-1000.

Kewalramani T, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103(10):3684-3688.

Kozopas KM, Yang T, Buchan HL, Zhou P, and Craig RW. MCL1, a gene expressed in programmed myeloid cell differentiation, has sequence similarity to BCL2. *Proc Natl Acad Sci U S A*. 1993:90;3516-3520.



Martin A, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica. 2008;93(12):1829-1836.

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine. 2008;27(13):2420-2439

Nooka AK., Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma.

http://www.bloodjournal.org/content/bloodjournal/early/2015/04/02/blood 2014 11 568923.full.pdf

Palumbo A, Anderson K. Multiple Myeloma. N Engl J Med 2011;364:1046-60

Peperzak V, Vikström I, Walker J, Glaser SP, LePage M, Coquery CM, et al. "MCL1 is essential for the survival of plasma cells." Nat Immunol 2013; 14(3): 290-297.

Philip T, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med. 1987;316(24):1493-1498.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-4695

Ravandi F. Relapsed acute myeloid leukemia: why is there no standard of care? Best practice & research 2013;26:253-9.

Ravandi F, Cortes J, Faderl S, et al. Characteristics and outcome of patients with acute myeloid leukemia refractory to 1 cycle of high-dose cytarabine-based induction chemotherapy. *Blood* 2010;116:5818-23; quiz 6153.

Robinson SP, et al. Autologous stem cell transplantation for relapsed/refractory diffuse large B-cell lymphoma: efficacy in the rituximab era and comparison to first allogeneic transplants. A report from the EBMT Lymphoma Working Party. Bone Marrow Transplant. 2016;51(3):365-371.

Sehn LH and Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.

Smith D, Yong K. Multiple myeloma. BMJ. 2013 Jun 26;346:f3863. doi: 10.1136/bmj.f3863. Review.

Smith D, Yong K. Multiple Myeloma. BMJ 2013;346:f3863 doi: 10.1136/bmj.f3863. Society AC. Cancer Facts and Figures, 2017. Atlanta, George, USA: American Cancer Society; 2017.

Strasser A, Cory S, and Adams JM. Deciphering the rules of programmed cell death to improve therapy of cancer and other diseases. *Embo j.* 2011:30;3667-3683.

Swerdlow SH, et al. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. Blood. 2016

Thall P, Simon R, Estey E. "Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes", Statistics in Medicine, vol 14, 357-379 (1995).

Thomas RL, Roberts DJ, Kubli DA et al. Loss of MCL-1 leads to impaired autophagy and rapid development of heart failure. *Genes Devel.* 2013;27:1365-1377.



### 41. Added Appendix K. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

			C	Frade		
Complication	0	1	2	3	4	5
Creatinine*, <sup>†</sup>	≤1.5 × ULN	1.5 × ULN	1.5 - 3.0 × ULN	> 3.0 - 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None		One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

### 42. Added Appendix L. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value		Change from Baseline
Uric Acid	$\geq$ 476 µmol/L (8 mg/dL)	-OR-	25% increase from baseline
Potassium	$\geq$ 6.0 mmol/L (6 mg/L)	-OR-	25% increase from baseline
Inorganic phosphorus	$\geq$ 1.45 mmol/L (4.5 mg/dL)	-OR-	25% increase from baseline
Calcium	$\leq$ 1.75 mmol/L (7.0 mg/dL)	-OR-	25% decrease from baseline

Note: Two or more elements with laboratory values out of range or changes from baseline.