16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan (Protocol No: AL-335-604) Version 1.0 dated 17-May-2017

STATISTICAL ANALYSIS PLAN

ALIOS BIOPHARMA
260 E. Grand Ave
South San Francisco, CA 94080

A Phase 2a, Open-Label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of the Combination of AL-335 and Odalasvir, with or without Simeprevir, in Treatment-Naïve Subjects with Genotype 1, 2 or 3 Chronic Hepatitis C infection with or without compensated Child Pugh A Cirrhosis

Protocol No: AL-335-604

SAP Version 1.0

SAP Date: 17 May 2017

Prepared by:

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inVentiv Health Clinical

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SIGNATURE PAGE

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Protocol No: AL-335-604

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
$AUC_{0\text{-last}}$	Area Under the Curve from time zero to last measurable plasma concentration
$AUC_{0\text{-}\tau}$	Area Under the Curve during one dosing interval
$AUC_{0\text{-inf}}$	Area Under the Curve from time zero to infinity
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C_{last}	Last measurable plasma concentration
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CI	Confidence Interval
CL/F	Apparent oral clearance
CRF	Case Report Form
CV	Coefficient of Variation
ECG	ElectroCardioGram
i.e.	id est
HCV	Hepatitis C Virus
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (synonymous with “study drug”)
IS	Included Set
λ_z	Apparent terminal elimination rate constant
LLN	Lower Limit of Normal range

Abbreviation	Definition
MedDRA®	Medical Dictionary for Regulatory Activities®
NCA	Non-Compartmental Analysis
PCSA	Potentially Clinically Significant Abnormalities
PK	PharmacoKinetics
PKS	PharmacoKinetic Set
PPS	Per Protocol Set
PT	Preferred Term
QRS	QRS interval duration
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
RAV	Resistance-Associated Variants
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response
$t_{1/2}$	Apparent terminal elimination half-life
TFLs	Tables, Figures, and Listings
t_{last}	Time corresponding to last measurable plasma concentration
t_{max}	Time to reach maximum plasma concentration

Abbreviation	Definition
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal range
VL	Viral load
Vz/F	Apparent volume of distribution
WBC	White Blood Cell
WHO	World Health Organisation

1. Introduction

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures and listings. It applies to the whole study on final analysis. Viral sequencing (e.g., Resistance-Associated Variants (RAV)) analyses will be described in a separate SAP.

2. Study objectives

2.1 Primary objective

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of AL-335 in combination with ODV with or without SMV in subjects with GT1 or GT2 or GT3 CHC infection in treatment-naïve subjects with or without compensated Child Pugh A Cirrhosis

2.2 Secondary objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy of treatment with AL-335 in combination with ODV±SMV in subjects with GT1 or GT2 or GT3 CHC infection
- To evaluate the pharmacokinetics of AL-335 (and metabolites), ODV±SMV in plasma
- To evaluate the dynamics of HCV RNA in subjects with GT1 or GT2 or GT3 CHC infection treated with AL-335 in combination with ODV±SMV
- To evaluate the effect of baseline host and disease-related characteristics on treatment outcome
- To evaluate the impact of the presence of an (NS) 3 polymorphism (e.g., Q80K; SMV-containing arms only) and/or NS5A and NS5B polymorphisms at baseline on treatment outcome
- To evaluate the viral resistance profile after ≤12 weeks administration of AL-335 in combination with ODV±SMV

3. Study methodology

3.1 Description of cohorts and groups (based on protocol version 8.1 of the 21st of December 2016)

Cohort #	GT	Cirrhosis	AL-335 dose (mg)	ODV dose (mg)	SMV dose (mg)	Duration (weeks)
1	1	N	400	50 QD	100	8
1b	1	N	800	50 QOD	--	8
2	1	N	800	50 QOD	75	8
3	1	N	800	50 QOD	75	6
4	1	N	800	50 QOD	--	8 (N=5) 12 (N=8)
5	3	N	800	50 QOD	75	8 (N=5) 12 (N=14)
6	1	Y	800	50 QOD	75	8
7	1	Y	800	25 QD	75	8
8	1	Y	800	25 QD	75	8
9	1	Y	800	25 QD	75	12
10	1	Y	800	25 QD	75	12
11	2	Y	800	25 QD	75	12
12	2	Y	800	25 QD	75	8
13-15	TBD					

Cohort #	Genotype	Cirrhosis	AL-335 dose (mg)	ODV dose (mg)	SMV dose (mg)	Duration (weeks)	Group*
1	1	No	400	50 QD	100	8	1
1b	1	No	800	50 QOD	-	8	1b+4
2	1	No	800	50 QOD	75	8	2
3	1	No	800	50 QOD	75	6	3
4	1	No	800	50 QOD	-	8 (N=5) 12 (N=8)	1b+4

5	3	No	800	50 QOD	75	8 (N=5) 12 (N=14)	5
6	1	Yes	800	50 QOD	75	8	6+7+8
7	1	Yes	800	25 QD	75	8	6+7+8
8	1	Yes	800	25 QD	75	8	6+7+8
9	1	Yes	800	25 QD	75	12	9+10
10	1	Yes	800	25 QD	75	12	9+10
11	2	Yes	800	25 QD	75	12	11
12	2	Yes	800	25 QD	75	8	12
13-15	To be determined						

*These are combined groups for presentation purpose of all data except pharmacokinetics,

3.2 Visit Windows and Phase Definitions

Phases will be constructed as follows:

Trial phase	**Start date**	**End date**
Screening (phase 0)	Minimum of Date of signing the informed consent and Date of the first screening visit	1 day before the first study drug intake (AL-335+ODV(±SMV))
Treatment (phase 1)	Date of first study drug intake (AL-335+ODV(±SMV))	Date of last study drug intake: MAXIMUM{Date of last study drug intake (AL-335+ODV(±SMV))} + 3 days*
Follow-up (phase 2)	End date of Treatment phase + 1	Trial termination date

*In case the last study drug intake is missing, other dates can be used instead for date of last study drug intake: E.g. if the subject discontinued treatment (known from the disposition table): date of the withdrawal visit, if the latter is not available: date of first available FU visit minus the number of days in follow-up at which this FU visit was scheduled according to the protocol. If those dates are not available, date of trial termination.

The number of days in the treatment phase (ADY) will be defined as:

ADY = visit date – date of first study drug intake +1 for visits on or after the day of first study drug intake

ADY = visit date – date of first study drug intake for visits before the day of first study drug intake

In case the date of first study drug intake is missing, the date of the baseline visit can be used as date of first study drug.

Actual End of Treatment visit (EOT) is defined as the last visit in the Treatment phase.

All visits (regardless the investigated parameter) will be allocated within each phase to analysis time points based on the number of days in phase (ADY):

6-Week Cohorts

Trial phase	**Target phase day**	**Analysis time point (numeric version)**	**Analysis time point**[b]	**Time interval (days)**[a]
Screening	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline	≤1
	2	0.2	Day 2	2
	3	0.3	Day 3	[3,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,18]
	21	3	Week 3	[19,25]
	28	4	Week 4	[26,32]
	35	5	Week 5	[33,39]
	42	6	Week 6	[40, + ∞]
	last visit while on study therapy or 3 days after the day of last dose	999	EOT	
Follow-up phase	25	16	Follow-up Week 4	[1,39]

	53	20	Follow-up Week 8	[40,67]
	81	24	Follow-up Week 12	[68,102]
	123	30	Follow-up Week 18	[103,144]
	165	36	Follow-up Week 24	[145, +∞]

8-Week Cohorts

Trial phase	Target phase day	Analysis time point (numeric version)	Analysis time point[b]	Time interval (days)[a]
Screening	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline	≤1
	2	0.2	Day 2	2
	3	0.3	Day 3	[3,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,18]
	21	3	Week 3	[19,25]
	28	4	Week 4	[26,32]
	35	5	Week 5	[33,39]
	42	6	Week 6	[40,46]
	49	7	Week 7	[47,53]
	56	8	Week 8	[54, +∞]
	last visit while on study therapy or 3 days after the day of last dose	999	EOT	
Follow-up phase	25	16	Follow-up Week 4	[1,39]
	53	20	Follow-up Week 8	[40,67]
	81	24	Follow-up Week 12	[68,102]
	123	30	Follow-up Week 18	[103,144]

	165	36	Follow-up Week 24	[145, +∞]

12-Week Cohorts

Trial phase	**Target phase day**	**Analysis time point (numeric version)**	**Analysis time point[b]**	**Time interval (days)[a]**
Screening	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline	≤1
	2	0.2	Day 2	2
	3	0.3	Day 3	[3,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,18]
	21	3	Week 3	[19,25]
	28	4	Week 4	[26,32]
	35	5	Week 5	[33,39]
	42	6	Week 6	[40,46]
	49	7	Week 7	[47,53]
	56	8	Week 8	[54,60]
	84	12	Week 12	[82, +∞]
	last visit while on study therapy or 3 days after the day of last dose	999	EOT	
Follow-up phase	25	16	Follow-up Week 4	[1,39]
	53	20	Follow-up Week 8	[40,67]

	81	24	Follow-up Week 12	[68,102]
	123	30	Follow-up Week 18	[103,144]
	165	36	Follow-up Week 24	[145, +∞]

[a] The reference day of the Treatment and Screening phase is the day of the first study drug intake (= day 1 in Treatment phase).

[b] Target day in follow-up phase equals target day in the protocol minus 3 days.

If two visits fall within the same interval, the last measurement within the interval will be used for the descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If there are two measurements on the same day and time, then the measurement with the highest sequence number will be used. Listings will include all values.

4. Statistical considerations

Efficacy and safety data will be analysed using SAS® software version 9.4 (SAS institute Inc. [redacted] USA).

Pharmacokinetic data from the PK substudy will be analysed using Phoenix® WinNonLin® version 6.4 (Pharsight) and SAS® software version 9.4 (SAS Institute Inc. [redacted] USA) for final analysis.

Descriptive statistics will be supplied according to the nature of the criteria:

- Quantitative variable: sample size, arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum, and quartiles if necessary (with geometric mean, arithmetic and geometric coefficients of variation (CV), and quartiles for PK parameters, geometric mean will not be reported in case of value equal to 0).
- Qualitative variable: sample size, absolute and relative frequencies per class. Percentages will be provided with one decimal place.

Safety data will be organized by cohort.

All safety and pharmacokinetics listings will be sorted by cohort, subject, and measurement time if applicable.

For all except pharmacokinetics data, cohorts that evaluate the same treatment regimen for the same duration (e.g., Cohort 1b and the first 5 subjects in Cohort 4) will be pooled (using Label “Cohort 1b+Cohort 4 (8 Weeks).” If multiple treatment durations and/or regimens were assessed in a single cohort, the data for that cohort will be presented separately (e.g. Cohort 4 (12 weeks) will be separate from Cohort 4 (8 weeks), which will be pooled with cohort 1b). For cohorts with different clinical characteristics (e.g. HCV genotype, cirrhosis status),

treatment regimens or same treatment regimen but with different durations, data will be presented separately.

For pharmacokinetic data, cohorts that evaluate the same treatment regimen (including study medications and doses) in the same population (cirrhotic vs non-cirrhotic), whatever the duration, or HCV genotype will be pooled, i.e. the presentation of cohorts will be:

- Cohort 1,
- Cohort 1b+4,
- Cohort 2+Cohort 3+Cohort 5,
- Cohort 6.
- Cohort 7+Cohort 8+Cohort 9+Cohort 10+Cohort 11+Cohort 12

Handling of missing and retest values

No management of missing data will be done, except for pharmacokinetic values (see section 7.1) and missing or incomplete start/stop dates (see below).

Missing start or end dates for events not aligned to a specific visit/week such as adverse events, medications reported, etc., will be imputed using the following rules:

- A completely missing start date of an event will be set to the date of the first dose of study medication, unless it is clearly indicated that this is an event happening pretreatment. In this case, it will be set to the day before the first dose of study medication.
- A completely missing stop date will not be imputed, but the event will be assumed to be ongoing.
- Partially missing dates where the year is known will be set to 01 January of that year or the first dose of study medication date, if the first dose of study medication occurred in that year.
- Partially missing dates where the year and month are known will be set to the first day of that month or the first dose of study medication date, if the first dose of study medication occurred in that month.

If, by applying the above rules, the stop date is imputed before the start date, then the stop date will be set to be the same as the start date.

For all parameters and for subjects with retest values, the last reliable value will be used as a measurement time before the first investigational medicinal product (IMP) administration (provided it was measured before IMP administration) and the first reliable value will be used as a measurement time after the first IMP administration.

Baseline definition

For all parameters, baseline will be defined as the last available (and reliable if applicable) single measurement prior to the first IMP administration unless otherwise specified (e.g. ECG).

Duration

Duration (in days, hh:mm) will be calculated as the difference between start and stop date and time (e.g. duration of AE (days, hh:mm) = date of AE end date and time – date of AE onset date and time).

Duration (in days) will be calculated as the difference between start and stop date + 1 (e.g. duration of a medication (days) = date of medication end date – date of medication onset date + 1).

Type I error rate

No significance testing will be performed. However, two-sided Clopper-Pearson 95% CI will be constructed around the proportion of subjects with sustained virologic response (SVRx) and other virologic response parameters, for each cohort.

5. Description of study subjects

5.1 Definition of analysis sets

The following analysis sets will be defined:

Included set (IS): all the subjects included in the study.

Safety/Efficacy/Intent-to-treat population (Safety set): All subjects enrolled into the study who have received at least one dose of any study drug, whether prematurely withdrawn from the study or not, will be included in the safety/efficacy/Intent-to-treat set.

Pharmacokinetic set (PKS): Will be comprised of all safety set subjects except those that they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

Per Protocol set (PPS): A per protocol analysis including all subjects enrolled and adherent to the protocol may be performed for certain efficacy analyses.

A subset of major protocol deviations, that may have an impact on the results of the analysis, will be identified prior to database lock. If there are a substantial number of subjects with such protocol deviations, a per-protocol analysis will be performed on the primary endpoint, based on subjects from the Safety set, excluding these subjects. Additional efficacy analysis using the PPS may be performed on an ad-hoc basis.

5.2 Subject disposition

A summary table with the description of the number of included subjects, the number of subjects who completed study and the number of subjects who discontinued classified by main reason of withdrawal will be performed by cohort and overall on the subjects included in the Included set. Corresponding individual listings will be provided.

A summary table with the description of the number and percentage of subjects in each analysis set (Safety set, and Pharmacokinetic set) will be performed by cohort and overall. A specific listing of subjects excluded from safety/efficacy and pharmacokinetic analyses will be provided with reason for exclusion.

A summary table with the number and percentage of subjects at each visit will be performed by cohort and overall on the subjects included in the safety set.

Listings with end of study status and study visit dates will also be carried out.

5.3 Protocol deviations

A summary table by cohort and overall with the number and percentage of subjects presenting deviations relating to inclusion/exclusion criteria (all eligibility criteria responses) will be prepared on the subjects included in the safety set. A summary table by cohort and overall with the number and percentage of subjects presenting other protocol deviations (all deviations judged relevant by the sponsor during the data-review meeting) will also be prepared. The corresponding listings will be provided with the status of deviation (minor/major, as assessed by the sponsor during the data-review meeting).

5.4 Definition of subgroups

The following subgroups will be considered to be investigated for efficacy; combinations of more than one subgroup may also be done. In case subgroup categories are smaller than 10 subjects within a cohort, subgroup categories might be combined.

- IL28B genotype (CC, CT, TT)
- HCV genotype/subtype (1a,1b, 1other, 2, 3)
- Prior treatment status (cirrhosis cohorts only) – prior pegylated interferon + ribavirin treatment with relapse

6. Demographic data and baseline characteristics

The analyses on demographic and other baseline characteristics will be performed on the safety set and PK set. Analyses on medical and surgical history, previous and concomitant medication, and compliance will be performed for the safety set.

Separate ad hoc summary tables of the demographic data and baseline characteristics for all subjects in cohorts 1b+4 (N=33) and cohort 5 (N=19) will be generated since, at the time of enrolment, all subjects in these two groupings were intended to dose for the same duration.

6.1 Demographic data

Subjects' demographic characteristics (age, sex, race, ethnicity, height, weight and BMI recorded at screening and Interleukin 28B genotype) will be summarised by cohort and overall, and listed.

6.2 Other baseline characteristics

HCV genotype as well as HCV RNA values at baseline (in IU/mL and $\log_{10}$ IU/mL) will be summarised by cohort and overall, and listed.

Serology testing will be listed.

Positive results of serology will be listed.

Childbearing status (for female only) and contraception method will be listed.

Alcohol consumption will be listed.

Information related to liver biopsy and fibroscan will be listed as well as Child-Pugh class assessment and hepatocellular carcinoma assessment (only for compensated cirrhosis cohort). Fibroscan score and Child-Pugh score will be summarised by cohort and overall.

6.3 Medical and surgical history

Information on medical and surgical history recorded at the screening visit will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.1.

A table with the number and percentage of subjects having at least one previous/ongoing medical and surgical history (except liver diseases) will be generated by cohort and overall. The same table will be provided for liver diseases (SOC: "Hepatobiliary disorders"). Previous/ongoing medical and surgical history (except liver diseases) and previous/ongoing medical and surgical history related to liver diseases will be listed separately.

6.4 Previous and concomitant medications

Information on previous and concomitant medications will be coded according to the WHO drug Dictionary (WHO-DD) version of June 2015.

A previous medication will be defined as a medication stopped prior to the date and time of first administration of IMP. A concomitant medication will be defined as a medication which is taken by subjects any time during the treatment period (on or after the date and time of first IMP administration for each subject).

Incomplete dates (i.e. day and/or month and/or year missing):

- In case of a partial start date, the therapies are allocated to the phases using the available partial information, no imputation is done. If, for instance, for a therapy start date only month and year is available, these data are compared with the month and year info of the phases.
- In case of a completely missing start date, the therapy is considered as having started before the trial. In case of a completely missing end date, the therapy is considered as ongoing at the end of the trial.
- In case of a partial end date, the therapies are allocated to the phases using the available partial information, no imputation is done. If, for instance, for a therapy end date only month and year is available and are the same as month and year of the first IMP administration, the therapy is considered as concomitant.

A table with the number and percentage of subjects having at least one previous medication will be generated by cohort and overall (overall and by Anatomical Therapeutic Chemical (ATC) and by preferred name). A table with the number and percentage of subjects having taken at least one concomitant medication will be generated by cohort and overall (overall and by Anatomical Therapeutic Chemical (ATC) and by preferred name). Previous and concomitant medications will be listed separately.

6.5 Compliance

A listing with IMP administration dates and times will be carried out for each study drug. Subjects that took additional doses (either extra doses on a dosing day (all drugs) or on

additional days other than those planned (for ODV QOD regimens) will be flagged in the listing. Time of meals intake will be listed as well.

7. Pharmacokinetic data

Two types of PK analysis will be performed for this study: 1) Non-compartmental analysis (NCA) for subjects participating in the PK substudy and 2) population PK in all subjects. This SAP will only cover the NCA PK analyses done in patients in the PK substudy. The population PK analysis will be described in a separate SAP and will have its own report.

The pharmacokinetic analysis will be performed on the pharmacokinetic set (PKS).

7.1 Generalities

The following rules for **PK parameters calculation** after each administration will be used:

Actual sampling times will be used for deriving PK parameters. In the case the actual sampling time will not be known, the scheduled time will be used, with appropriate footnoting. Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time (i.e., >20.00% deviation from the scheduled time), this plasma concentration will be excluded from descriptive statistics in the plasma concentration table and reported in the CSR.

If an entire concentration-time profile is below the limit of quantification (BLQ), the profile will be excluded from the PK analysis.

All BLQ values will be replaced by “0”.

All embedded BLQ values (BLQ value between two measurable concentrations) will be treated as missing. Details of this exclusion must be documented in the clinical study report.

For the determination of λ_z, only those data points judged to describe the terminal log-linear decline resulting in an adjusted coefficient of determination value > 0.9 will be used in the regression. A minimum of 3 data points will be used in calculating λ_z (excluding $C_{max)}$. The number of points and the lower and upper limits of the terminal phase will be identified in the study data and in the CSR.

If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous or to introduce a substantial bias, they will be set to missing and excluded from the PK analysis.

The following rules for **plasma concentration versus time graphic representation** will be used:

No graphic representation will be made if all values are BLQ.

All BLQ values will be replaced by “0”.

All BLQ values will not be shown on semi-logarithmic plots.

Profiles and individuals values considered to be outliers should be included in the individual plots and excluded in the mean plots.

Actual sampling times will be used for individual subjects PK profiles and nominal sampling times should be used for mean plots.

All subjects will be plotted with the same scale and range of values on the x- and y-axes

The following rules for **mean plasma concentration calculation** will be used:

If more than half (>50%) of the values at a single time point are BQL, mean and median values will be reported as BQL. Standard deviation and %CV will not be reported; maximum and minimum values will be reported as observed (including BQL).

If more than (or equal) half of values are not BLQ: statistics will be calculated considering BLQ values as zero.

For **summary statistics for PK parameters**:

If more than (or equal to) half of values are available: statistics will be calculated considering available values.

If less than half of values are present: mean will not be calculated and presented as missing. Min, median and max value on available values will be presented.

All concentrations below the limit of quantification or missing data will be labelled as such in the concentration data listings.

7.2 Plasma pharmacokinetic concentrations and parameters

7.2.1 Plasma pharmacokinetic parameters

Blood samples will be drawn for AL-335, SMV and ODV (depending on the cohorts) on:

- On Day 1 at 0 hour,
- On Week 2 at 0, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 hours (For PK substudy only),
- On Week 3 at 0, 2-4 hours,
- On Week 4 at 0, 6-8 hours,
- On Week 6 at 0, 2-4 hours,
- On Week 8 at 0, 6-8 hours (8 or 12 Week Cohorts),
- On Week 10 at 0, 2-4 hours (12 Week Cohorts),
- On Week 12 at 0, 6-8 hours (12 Week Cohorts).

For subjects in the PK substudy, relevant plasma pharmacokinetic (PK) parameters will be calculated for AL-335 and its metabolites (ALS-022399 and ALS-022227), SMV and ODV by standard non-compartmental methods for those subjects with sufficient plasma concentration data. The rules defined in the previous section 7.1 will be used.

The different areas under the concentration-time curve (AUC) will be calculated using the linear Trapezoidal summation (both ascending and descending phase).

The following plasma pharmacokinetic parameters will be calculated for AL-335 and its metabolites (ALS-022399 and ALS-022227), SMV and ODV:

Parameters (unit)	Definition
C_{min} (unit)	Minimum observed plasma concentration
C_{max} (unit)	Maximum observed plasma concentration
C_{trough} (unit)	Concentration at the end of a dosing interval before the next dose administration (Pre-dose or C_{0h})
t_{max} (h)	Time to reach maximum plasma concentration
$AUC_{0\text{-}last}$ (unit.h)	Area under the plasma concentration-time curve from time zero to last measurable (Non-BLQ) plasma concentration In cases where a subject's $AUC_{0\text{-}last}$ is estimated over a time interval that is very different from that of the other subjects in the group, it is recommended that subject's $AUC_{0\text{-}last}$ could be excluded from the calculation of descriptive statistics. All exclusions must be clearly documented in the CSR. In cases where more than half of subjects have a different t_{last}, it may not be appropriate for the descriptive statistics for $AUC_{0\text{-}last}$ to be reported.
$AUC_{0\text{-}24}$ (unit.h)	Area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{0\text{-}48}$ (unit.h)	Area under the plasma concentration-time curve from time zero to 48 hours (only for ODV and QOD cohorts)
$C_{ss,avg}$	Average concentration of the drug calculated as follows: $C_{ss,avg} = AUC_{0\text{-}\tau} / \tau$
C_{last} (unit)	Last observed plasma concentration
t_{last} (h)	Time to reach last plasma concentration

7.2.2 Plasma pharmacokinetic analysis

Listings with plasma concentrations of AL-335, ALS-022399 and ALS-022227, SMV and ODV (including PK blood sampling dates and times) and PK parameters will be provided by cohort, dose, and subject. These listings will be performed on all subjects with an available profile (complete or incomplete), including those who are excluded from the PKS.

A specific listing will be also done focussing on subjects who either discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event.

Individual plasma concentrations for all subjects and PK parameters of AL-335, ALS-022399 and ALS-022227, SMV and ODV including descriptive statistics for subjects participating in the PK substudy will be presented in tables by cohort and by pooled cohorts.

Graphs for plasma concentration versus time profiles of AL-335, ALS-022399 and ALS-022227, SMV and ODV will be generated on linear and log/linear coordinates for arithmetic mean (±SD) by cohorts.

In addition, the plasma concentration versus time profiles of AL-335, ALS-022399 and ALS-022227 will also be presented on the same graph or as a separate graph on linear and log/linear coordinates for arithmetic mean (±SD) by pooled cohort.

Moreover, the plasma concentration versus time profiles of AL-335, ALS-022399 and ALS-022227, SMV and ACH-3102 will be presented graphically on linear and log/linear coordinates for each subject.

Pre-dose ("trough") concentrations of AL-335, ALS-022399 and ALS-022227, SMV and ODV for all subjects at all available timepoints will be presented graphically on linear coordinates for arithmetic mean (±SD) by cohorts and by pooled cohorts.

Scatter plots will be generated for the comparison of C_{trough}, C_{max}, and $AUC_{0-\tau}$ parameters of AL-335, ALS-022399, ALS-022227, SMV and ODV by cohorts and by pooled cohorts.

8. Safety data

The safety analyses will be performed on the safety set.

8.1 Adverse events

Adverse events, including pre-treatment events, will be recorded from the time of consent through the completion visits, for the treatment and follow-up phase combined.

Adverse events will be coded according to MedDRA® Version 19.1.

A treatment-emergent adverse event (TEAE) is an adverse event that occurs after the first IMP administration or that was present prior to dosing but exacerbated after the first IMP administration.

Adverse events will be summarised in tables as follows (overall and by System Organ Class (SOC) and Preferred Term (PT)):

- Number and percentage of subjects with at least one adverse event and number of adverse events for each cohort,
- Number and percentage of subjects with at least one TEAE and number of TEAEs for each cohort,
- By intensity, with the number and percentage of subjects with at least one TEAE and number of TEAEs for each cohort,
- By causality of each treatment, with the number and percentage of subjects with at least one TEAE and number of TEAEs for each cohort.

Moreover, an overall summary table of all TEAEs will be presented.

In addition, summary tables will also be presented for TEAEs, serious TEAEs, TEAEs leading to any study drug discontinuation, severe or life threatening (i.e. Grade 3 / 4) TEAEs, and TEAEs with fatal outcome by decreasing frequency of PT.

The incidence and comparable prevalence rate per 2-week time interval for any AEs will be summarized and plotted by cohort.

Note: Repetitions will only be counted once in summary tables. Repetitions are defined as follows: if a given subject presents several adverse events with the same preferred term during the same phase (treatment and follow-up phase combined), only one event is counted, the others are considered repetitions or recurring episodes. The start time of the event will be the start time of the first occurrence, the end time will be the end time of the last episode. The intensity will be the highest recorded intensity for all episodes. The causality will be the highest likelihood recorded for all episodes.

A summary table of TEAEs of special interest (cardiac events, increased bilirubin (hyperbilirubinemia, blood bilirubin increased), rash and photosensitivity) will be also presented (see Appendix 4 for detailed list of SMQs).

The incidence rates for each event of interest by WHO toxicity grades and relationship to study drugs will be summarized. Time to the first occurrence of the events of interest will be summarized and Kaplan-Meier curves will be plotted.

The incidence and comparable prevalence rate per 2-week time interval for AEs of special interest will be summarized and plotted by cohort.

Bar graphs of the worst toxicity grade of cardiac events over time by cohort will be plotted.

All adverse events for subjects who met the Study Stopping Rules(i.e. <1 log decline in HCV RNA after 4 weeks of treatment) will be listed.

All TEAEs reported in the CRF will be listed with the SOC, PT and investigator's verbatim. Additional listings will be provided for serious adverse events (SAEs), TEAEs with grade 3 or grade 4, TEAEs leading to any study drug discontinuation, TEAEs of special interest, and TEAEs with fatal outcome.

In case of rash, all information related to rash assessments will be listed.

8.2 Clinical laboratory data

The following clinical laboratory parameters will be measured (see section 12.1):

- At the screening visit,
- On Day 1, Week 1, Week 2, Week 4, Week 6, Week 8 (8 or 12 Week Cohorts), Week 10 (12 Week Cohorts), Week 12 (12 Week Cohorts), safety follow-up visit.

Additional measurements are done on Week 3, Week 5 and Week 7 for alanine aminotransferase (ALT) and aspartate aminotransferase.

Haematology parameters will be listed and grouped as follows:

- Red blood cells: haemoglobin (g/L), haemoglobin A1C (mmol/mol) only at screening, hematocrit (fraction of 1), mean corpuscular haemoglobin (MCH) (fmol), mean corpuscular

haemoglobin concentration (MCHC) (mmol/L), mean corpuscular volume (MCV) (fL), mean platelet volume (MPV) (fl), erythrocyte sedimentation rate (mm/h), red distribution width (RDW) (%), reticulocytes (G/L and %) and red blood cell count (RBC) (T/L).

- White blood cells: basophils (G/L and %), eosinophils (G/L and %), lymphocytes (G/L and %), monocytes (G/L and %), neutrophils (G/L and %)) and white blood cell count (WBC) (G/L).

- Platelets (G/L).

Blood chemistry parameters will be listed and grouped as follows:

- Liver function: alanine aminotransferase (ALT) (IU/L), alkaline phosphatase (IU/L), aspartate aminotransferase (AST) (IU/L), total bilirubin (µmol/L) and direct bilirubin (µmol/L).

- Renal chemistry: creatinine (µmol/L) and blood urea nitrogen (BUN) (mmol/L).

- Electrolytes: calcium (mmol/L), chloride (mmol/L), phosphorus (mmol/L), potassium (mmol/L), sodium (mmol/L) and bicarbonates (mmol/L).

- Metabolism parameters: glucose (mmol/L), cholesterol (mmol/L), triglycerides (mmol/L), lipase (IU/L), uric acid (µmol/L) and lactate dehydrogenase (LDH) (IU/L).

- Other parameters: albumin (g/L), creatine kinase (CPK) (IU/L), total protein (g/L), alpha fetoprotein (ug/L) only at screening, Alpha-1 Acid Glycoprotein (g/L) only at screening, Beta natriuretic peptide (BNP) and NT-pro-BNP.

Coagulation parameters will be listed and grouped as follows:

- Coagulation parameters: prothrombin time (PT) (s), activated partial thromboplastin time (aPTT) (s) and international normalized ratio (INR).

Urinalysis parameters will be listed and grouped as follows:

- Planned urinalysis parameters: dipstick determination of pH, specific gravity, glucose, bilirubin, ketones, leukocytes, nitrite, occult blood, protein and urobilinogen.

- Direct microscopy: in case of abnormal urinalysis parameters (in listing only).

Hormonology parameters will be listed as follows: FSH (IU/L) and estradiol (pmol/L)

In case a laboratory test result is *censored* (no numeric value is available, but only a verbatim term), the following rules are applied:

- $< x$ or $> x \rightarrow$ a numeric value will be imputed by a value exceeding the cut-off value with one unit.
- $\leq x$ or $\geq x \rightarrow$ imputation by x.

Laboratory values will be graded based on the following toxicity grading scale: The Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs ("DAIDS grading table", version of November 2014), Appendix F - protocol version 8.0 of the 13rd of September 2016.

Lab values will also be graded based on WHO grading scale, but summary tables will be based on DAIDS grading scale only.

For haematology, blood chemistry, and coagulation, raw data and changes from baseline (Day 1) if applicable will be described by measurement time, for each cohort.

For all lab parameters with toxicity grade, a summary table with the number and percentage of subjects with treatment emergent grade 1-4 and 3+4 will be generated for each cohort for the worst post-baseline value. The same table will be provided by measurement time.

For haematology and blood chemistry, graphs of individual subject values (spaghetti plots) will be generated for each cohort for the following parameters: ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, CPK, BNP, haemoglobin, platelets and white blood cells.

A listing of all values of a parameter over time for any parameter with treatment emergent Grade 3 or 4 will be generated. A listing of all values of a parameter over time for any parameter with treatment emergent abnormal values will be also generated.

Values will be listed (raw data and change from baseline) and laboratory abnormal values will be flagged with their toxicity grades and clinical significance information.

For urinalysis, raw data will be described by measurement time, for each cohort.

Urinalysis values will be listed including direct microscopy if any.

Hormonology parameters will be listed only.

For applicable lab parameters, cross-tabulation of the worst toxicity grades versus baseline will be presented, Plots of mean(SE), mean(SE) of change from baseline by cohort over time and Bar graphs of the treatment emergent abnormality by toxicity grade over time for selected laboratory parameters will be plotted.

In determining DAIDS toxicity grades the following rules are applied:

- The worst grades/abnormalities are determined over the whole observational period, including all post-reference scheduled and unscheduled measurements.
- The abnormalities “abnormally low” and “abnormally high” are considered equally important, i.e. if a subject has an “abnormally low” as well as an “abnormally high” post-reference value, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)
- If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations and in the ADaM database.

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the CTP will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

Definition treatment-emergent: An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent in a particular phase if it is worse than the reference. If the reference is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at reference to "abnormally high" post reference (or vice versa) is also treatment-emergent.

8.3 Other safety parameters

8.3.1 Vital signs data

Blood pressures (diastolic [DBP] and systolic [SBP]; mmHg), respiratory rate (breaths/min), body temperature (°C) and pulse rate (bpm) will be measured (see section 12.1) for each cohort at the screening visit, Day 1, Week 1 and then once a week thereafter.

Raw data and changes from baseline (Day 1 pre-dose) will be described by measurement time, for each cohort.

A summary table with the number and percentage of subjects with PCSA values (defined in section 12.2) will be generated by measurement time, for each cohort.

A specific listing of all values of a parameter over time for any parameter with PCSA values with clinical significance information will be generated.

Pulse rate, DBP, and SBP are classified in the following abnormality codes:

	Pulse (bpm)	**DBP (mmHg)**	**SBP (mmHg)**
Abnormally low	≤ 50	≤ 50	≤ 90
Abnormally high	≥ 120	-	-
Grade 1 or mild	-	> 90 - < 100	> 140 - < 160
Grade 2 or moderate	-	≥ 100 - < 110	≥ 160 - < 180
Grade 3 or severe	-	≥ 110	≥ 180

A summary table with the number and percentage of subjects with abnormal values (as defined above) will be generated for each cohort for the worst post-baseline value. The same table will be provided by measurement time.

A specific listing of all values of a parameter over time for any parameter with abnormal values with clinical significance information will be generated.

Values (raw data and changes from baseline) will be listed and PCSA and abnormal values will be flagged with clinical significance information.

Graph of mean (SE) by cohort over time will be plotted.

In determining the abnormalities, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period, including post-baseline scheduled and unscheduled measurements.

- The abnormalities ‘abnormally low’ and ‘abnormally high’/grades are considered equally important, i.e. if a subject has an ‘abnormally low’ as well as an ‘abnormally high’ or graded post-baseline value, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%.)

Definition treatment-emergent:

An abnormality will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from ‘abnormally low’ at baseline to ‘abnormally high’ or ‘grade 1’ or ‘grade 2’ or ‘grade 3’ post baseline (or vice versa) is also treatment-emergent.

8.3.2 Electrocardiogram data

Standard 12-lead ECG parameters (including heart rate (bpm), PR interval (ms), QRS duration (ms), QT interval (ms), Bazett QTc interval (QTcB; ms) and Fridericia QTc interval (QTcF; ms)) from both automatic and centrally read data, information on T- (normal or abnormal) and U-waves (normal or abnormal) and ECG abnormality will be measured (see section 12.1) for each cohort at the screening visit, Day 1, Week 1 and then once a week thereafter.

The mean of the triplicate ECGs will serve as analysable data for each visit. If one or more assessment is missing/not done then the mean will be calculated using the available assessments.

Centrally read data will be used for summary statistics and both locally and centrally read data will be listed.

Raw data and changes from baseline (Day 1 pre-dose) (except for T-and U-wave and ECG abnormality) will be described by measurement time, for each cohort.

A summary table with the number and percentage of subjects with PCSA values (defined in section 12.2) will be generated by measurement time, for each cohort.

Graphs of individual subject values (spaghetti plots) will be generated for each cohort for the following parameters: PR, QRS, QTcB, and QTcF. These graphs will include indications for the most conservative upper and lower limit of normal.

A specific listing of all values of a parameter over time for any parameter with PCSA values with clinical significance information will be generated.

A listing of all values over time for subjects with any clinically significantly abnormal ECGs will also be generated.

A listing of subjects with potentially progressive PR prolongation will be generated.

Potentially progressive PR prolongation is defined as any subject who has a post-baseline change of >20 ms from the highest pre-dose value.

Values (raw data/T- and U-wave/ECG abnormalities and changes from baseline) will be listed and data out of PCSA range will be flagged with clinical significance information.

The following abnormality categories are defined:

Abnormality Code	ECG parameter			
	HR	PR	QRS	$QT_{corrected}$ *
Abnormalities on actual values				
Abnormally low	≤50 bpm	<120 ms	NA	-
	≥120 bpm	]200-240] ms	>120 ms	-
Abnormally high		]240-300] ms		
		>300 ms		
Borderline:]450 ms, 480 ms]	-	-	-	450 ms< QTc ≤480 ms
Prolonged:]480 ms, 500 ms]	-	-	-	480 ms< QTc ≤500 ms
Pathologically prolonged: >500 ms	-	-	-	QTc>500 ms
Abnormalities on increase from baseline				
	-	[30; 60] ms	-	[30; 60] ms
	-	>60 ms	-	>60 ms

* QTcB or QTcF

A summary table with the number and percentage of subjects with abnormal values (as defined above) will be generated for each cohort for the worst post-baseline value. The same table will be provided by measurement time.

A specific listing of all values of a parameter over time for any parameter with abnormal values with clinical significance information will be generated.

A specific listing of all overall interpretations over time for any subject with any overall interpretation considered to be clinically significantly abnormal will be created.

In determining the abnormalities, the following rules are applied:

- Worst abnormalities are determined over the whole observational period, including post-baseline scheduled and unscheduled measurements.
- The abnormalities ‘abnormally low’ and ‘abnormally high’ are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

Cross-Tabulation of the worst ECG abnormalities in actual value versus the baseline value and Cross-Tabulation of the worst QTc increase versus the abnormality on the actual value will be presented.

Graphs of actual mean(SE), mean of change from baseline(SE) by cohort over time will be plotted. Spaghetti plots of PR for the patients who had prolonged PR interval or AV block (grade>=1) will be plotted.

Definition treatment-emergent:

An abnormality will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from ‘abnormally low’ at baseline to ‘abnormally high’ or ‘grade 1’ or ‘grade 2’ or ‘grade 3’ post baseline (or vice versa) is also treatment-emergent.

8.3.3 Other safety parameters

Echocardiograms will be performed at regular intervals and according to a standard protocol.

The centrally read echocardiogram results will be used for analysis.

The maximum decline in mean ejection fraction (EF) from baseline will be summarized in a table by cohort with the following cutoffs: decline of >10%, decline of >5-≤10% and decline of >0-<=5%. Moreover, the number of subjects with any mean EF that declines by >10%, >5-≤10% or >0-<=5% will be summarized by measurement time and cohort.

A listing of all mean EFs by time point for subjects with any mean EF that declines by >10% or >5-≤10% will be provided.

Moreover, for the following parameters: diastolic volume, left ventricular ejection fraction (LVEF) single plane, LV fractional shortening, LVPW diastolic thickness, systolic volume and ventricular septum diastolic thickness, the following analyses will be performed:

Raw data and changes from baseline (Screening) as well as percent changes from baseline will be described by measurement time, for each cohort.

Graphs of individual subject values (spaghetti plots) will be generated for each parameter and each cohort.

A summary table with the number and percentage of subjects with abnormally low, normal, and abnormally high values will be generated by measurement time, for each cohort.

Overall interpretation of echocardiograms will be listed by time point by cohort.

Graphs of actual mean(SE), mean of change from baseline(SE) by cohort over time will be plotted for mean ejection fraction.

Weight and BMI will be measured (see section 12.1) for each cohort at the screening visit and at the completion visits.

Raw data and changes from baseline (Day 1) will be described by measurement time, for each cohort and listed.

Complete physical examination will be measured (see section 12.1) for each cohort at the screening visit, on Day 1, Week 1 and then once a week after.

Results from physical examination will be described by measurement time, for each cohort.

All physical examinations over time for any subject with any clinically significantly abnormal physical examinations will be listed as well as all individual data.

Pregnancy test will be performed (see section 12.1) for each cohort at the screening visit and at the completion visits.

Positive pregnancy test will be listed as well as all individual data.

Toxicology testing will be listed.

9. Efficacy data

All efficacy analyses will be performed on the Safety set and, if necessary only, on the Per Protocol set.

9.1 Analysis Specifications

9.1.1 Level of Significance

No significance testing will be performed. However, a two-sided Clopper-Pearson 95% CI will be constructed around the proportion of subjects with SVRx and other virologic response parameters, for each cohort.

9.1.2 Data Handling Rules

Plasma HCV RNA values will be determined using the Roche Cobas Ampliprep/Cobas Taqman v2.0 assay with a lower limit of quantification (LLOQ) of 15 IU/mL and a limit of detection (LOD) of 15 IU/mL.

For the purpose of the analysis HCV RNA results "HCV RNA <15 IU/mL" will be imputed by LLOQ-1 IU/mL = 14 IU/mL before log transformation and "HCV RNA not detected" will be imputed by LOD-2 IU/mL= 13 IU/mL before log transformation.

9.2 Primary Efficacy Endpoint

The primary efficacy endpoint is sustained virologic response 12 weeks after the actual end of treatment (SVR12).

9.2.1 Definition

SVR12 is classified as success or failure according to the following algorithm based on HCV RNA values 12 weeks after the actual end of treatment.

***SVR12* is classified as a success (1) if** at the time point of SVR12, HCV RNA value(s) meet one of the following:

- HCV RNA Not detected or
- < LLOQ detected and
  - the sample is a confirmation* visit or
  - the sample is the last available HCV RNA measurement or
  - at the next available measurement, HCV RNA not detected or HCV RNA < LLOQ detected
- ≥ LLOQ and
  - the sample is not from a confirmatory visit* and
  - not the last available measurement in the study and
  - a next measurement is available and HCV RNA not detected or HCV RNA < LLOQ detected for this next measurement

Otherwise SVR12 is classified as a failure (0).

* Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

Time point of SVR12:

- 12 weeks after the actual EOT (i.e. the last available measurement in the SVR12 analysis window)
- or, if not available, the first available measurement at least 12 weeks after the actual EOT (i.e. the first available measurement after the SVR12 analysis window)
- or, if not available (i.e. no measurement at least 12 weeks after the actual EOT), the subject is considered a failure.

9.2.2 Analysis Methods

The number and proportion of subjects with SVR12 will be tabulated overall and by cohort, a two-sided Clopper-Pearson 95% CI will be constructed.

9.3 Major Secondary Endpoints

Secondary efficacy endpoints include:

- Proportion of subjects with SVR4, SVR18 and SVR24
- Change from baseline in $\log_{10}$ HCV RNA
- Actual values of $\log_{10}$ HCV RNA
- Proportion of subjects with on-treatment virologic response at all timepoints (HCV RNA not detected; HCV RNA < LLOQ detected; HCV RNA not detected or HCV RNA < LLOQ detected)
- Proportion of subjects with failure
- Proportion of subjects with on-treatment failure
- Proportion of subjects with viral relapse

9.3.1 Definitions

SVR4, SVR18 and SVR24 are defined similarly as SVR12 but with 4 weeks, 18 weeks and 24 weeks respectively, instead of 12 weeks.

In addition, for SVR24, the time point of SVR is defined as follows:

- 24 weeks after actual EOT (i.e. the last available measurement in follow up Week 24 analysis window)
- or, if not available, the first measurement available, after the follow-up Week 24 analysis window
- or, if not available, the last measurement available in the SVR18 analysis window, on condition that the time point of SVR24 has been reached

- or, if not available, the last measurement available in the follow up Week 12 analysis window (on condition that the time point of SVR24 has been reached)
- or, if not available, the subject is considered as not having SVR24

For SVR18, the timepoint of SVR is defined as follows:

- 18 weeks after the actual EOT (i.e. the last available measurement in follow up Week 18 analysis window)
- or, if not available, the subject is considered as not having SVR18

On-Treatment failure is defined as subjects who did not achieve SVR12 and with confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment. Includes subjects:

- With viral breakthrough, defined as a confirmed increase of >1 log10 in HCV RNA from nadir, or confirmed HCV RNA of >100 IU/mL in subjects whose HCV RNA had previously been <LLOQ while on treatment.
- With inadequate virologic response, defined as <1 log10 decline from baseline in HCV RNA after 4 weeks of treatment
- Who do not experience viral breakthrough or inadequate virologic response and have confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment (e.g., completed study drug treatment, discontinued due to adverse events, withdrawal of consent).

Viral Relapse is defined as follows**:**

Subjects who achieved HCV RNA <LLOQ at the actual end of study drug treatment and developed HCV RNA ≥LLOQ during post-treatment follow up.

Failure (No SVR12): Subjects who did not achieve SVR12, including:

- On-treatment failure (see above)
- Post-treatment failure, including subjects with:
  - Viral relapse (see above)
  - Missing HCV RNA at time point of SVR12

On-treatment virologic response:

Virologic response is quantitative HCV RNA concentration <LLOQ at any timepoint post-first dose of study drug. An SVR is HCV RNA <LLOQ at Weeks 4, 8, 12, 18 or 24 after cessation of study treatment.

Time to virologic response is defined as the number of days since the first day of medication intake until the first day that the threshold was achieved. The following thresholds are considered:

- HCV RNA Not Detected

- HCV RNA Not Detected or HCV RNA <LLOQ Detected

9.3.2 Analysis Methods

The efficacy analysis will be performed on the Safety set and Per Protocol set, by cohort.

Descriptive statistics per cohort and per time point for the continuous parameter (actual values and changes from baseline in $\log_{10}$ IU/mL HCV RNA) will be calculated.

Tabulations (numbers and proportions) per cohort and per time point for the categorical parameters will be provided. The observed proportion of subjects with SVR4 and SVR24 will be analyzed in the same way as the primary endpoint.

The influence of early virologic response parameters on SVR12 will be explored.

In addition, the reason for failure will be explored by type of failure (see definition of failure above). If more than one type of failure occurs, the order as presented below should be respected:

a) viral relapse

b) viral breakthrough

c) confirmed detected at EOT

d) missing at time point of SVR

Graphs of individual subject values (spaghetti plots) will be generated for each cohort for the viral load (VL) over time.

Graphs for mean VL change from baseline (+/- SD) over time will be generated for each cohort.

10. Reporting conventions

All tables, figures and listings are detailed in section 12.3. They will be prepared using SAS® software as rtf files and the rtf files will be compiled as Word files (one Word file by main section).

The footers will be presented as follows: --- STUDY <study protocol code> / <name of the program>.SAS / <name of the output>.RTF / DDMMMYY HH:MM ---.

Table and Listing Page Set Up Requirements:

- Font Type = Courier New
- Font Size = 8 pt (at a minimum)
- Page Margins: Top=2 cm; Bottom=2 cm; Left=2 cm; Right=2 cm
- Paper Size = A4 (21 cm x 29.7 cm)
- Page Orientation: Landscape
- Graphs: Portable Network Graphics (PNG) format

Summary statistics will be presented as follows.

Parameter (unit)	Statistics / Category	Group X (N=xx)
Quantitative variable*	n	xx
	Mean ± SD	xx.xx ± xx.xx
	SEM	xx.xx
	Median	xx.xx
	Min ; Max	xx.x ; xx.x
Qualitative variable	Class 1 (n,%)	xx (xx.x)
	Class 2 (n,%)	xx (xx.x)
	…	…

* For demographics and Baseline characteristics and for Safety summary tables:

All statistics, except the minimum and the maximum, will be provided with an additional decimal compared to the variable itself.

For PK summary tables:

- if n=1 or n=2, do not display other statistics than n
- For tmax, only minimum, median, maximum and number of observations will be reported.
- For calculated values, PK parameters and descriptive statistics up to, but not including 100, display to 3 significant figures, for example:
    - 0.35769 is reported 0.358
    - 3.5769 is reported 3.58
    - 35.769 is reported 35.8
    - 357.69 is reported 358
    - For values ≥ 1000, the whole integer is reported (example 3576.9 is reported as 3577)

t_{max} and t_{lag} values are to be reported to 2 decimal places; half-life is to be reported to 1 decimal place.

Coefficient of Variation is reported to 1 decimal place.

Ratios and confidence interval are reported to 2 decimal places.

Drug concentration data that could not be obtained will be listed as NS (No Sample) in data tabulations.

11. Appendices

11.1 Appendix 1 - Schedule of assessments of the study

Table 6-1. Schedule of Events for 8 or 12*-Week Treatment Groups

Interval / Assessments	Day				Week**							
	Screen -50 to -1	1	2	3	1	2	3	4	5	6	7	8
AL-335±ODV±SMV [1]		<----------										---------->
Obtain informed consent before study procedures	X											
Demographics	X											
Height, Weight, BMI[2]	X											X [2]
Drug Screen	X											
Medical History	X											
Echocardiogram	X (-3 days)							X (+3 days)				X (+3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X	X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X	X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X											
Alpha-fetoprotein, glycosylated HbA1C	X											
Liver Ultrasound (subjects with cirrhosis, if results from within the past 6 months are not available)	X											
HCV genotype	X											
IL28B genotype		X										
Randomization [4]		**X**										
AE & Conmed Evaluation	X	X	X	X	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.
[2] Weight only collected at last treatment visit.
[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.
[4] Randomization may take place up to 4 days before first dose.

Table 6-1. Schedule of Events for 8 or 12*-Week Treatment Groups

Interval / Assessments	Day				Week**							
	Screen -50 to -1	1	2	3	1	2	3	4	5	6	7	8
PK Samples [5]		X				X	X	X		X		X
Hematology [6]	X	X			X	X		X		X		X
Serum Chemistries [6]	X	X			X	X		X		X		X
Urinalysis	X	X			X	X		X		X		X
ALT/AST [6]	X	X			X	X	X	X	X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [9]	X							X				X
Stored serum sample [10]	X	X			X	X	X	X	X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335 (and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Weeks 3 and 6, 2-4 hours postdose, and at Weeks 4 and 8, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] Heterosexually active women of childbearing potential. A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* If a 12-week regimen is evaluated, the Week 5, 6, 7, and 8 visits will be repeated at Weeks 9, 10, 11, and 12, respectively.

** Weekly visit may occur ±1 day from the expected visit date.

Table 6-2. Schedule of Events for a 6-Week Treatment Group

Interval / Assessments	Day				Week*					
	Screen -50 to -1	1	2	3	1	2	3	4	5	6
AL-335+ODV±SMV [1]		<----------								---------->
Obtain informed consent before study procedures	X									
Demographics	X									
Height, Weight, BMI [2]	X									X [2]
Drug Screen	X									
Medical History	X									
Echocardiogram	X (±3 days)							X (±3 days)		X (±3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X									
Alpha-fetoprotein, glycosylated HbA1C	X									
Liver Ultrasound (subjects with cirrhosis, if results from within the past 6 months are not available)	X									
HCV genotype	X									
IL28B genotype		X								
Randomization [4]		X								
AE & Conmed Evaluation	X	X	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.

[2] Weight only collected at Week 6.

[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.

[4] Randomization may take place up to 4 days before first dose.

Table 6-2. Schedule of Events for a 6-Week Treatment Group

Interval / Assessments	Day				Week*					
	Screen -50 to -1	1	2	3	1	2	3	4	5	6
PK Samples [5]		X				X	X	X		X
Hematology [6]	X	X			X	X		X		X
Serum Chemistries [6]	X	X			X	X		X		X
Urinalysis	X	X			X	X		X		X
ALT/AST [6]	X	X			X	X	X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X	X	X
Pregnancy Test [9]	X							X		
Stored serum sample [10]	X	X			X	X	X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335(and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Weeks 3 and 6, 2-4 hours postdose, and at Week 4, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* Weekly visit may occur ±1 day from the expected visit date.

Table 6-3. Schedule of Events for a 4-Week Treatment Group

Interval / Assessments	Screen -50 to -1	Day 1	Day 2	Day 3	Week 1*	Week 2*	Week 3*	Week 4*
AL-335+ODV±SMV [1]		<--						-->
Obtain informed consent before study procedures	X							
Demographics	X							
Height, Weight, BMI [2]	X							X [2]
Drug Screen	X							
Medical History	X							
Echocardiogram	X (+3 days)							X (+3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X							
Alpha-fetoprotein, glycosylated HbA1C	X							
Liver Ultrasound (subjects with cirrhosis, if results from within the past 6 months are not available)	X							
HCV genotype/subtype	X							
IL28B genotype		X						
Randomization [4]		**X**						
AE & Conmed Evaluation	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.

[2] Weight only collected at Week 4.

[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits. Vital signs will be collected at all visits indicated.

[4] Randomization may take place up to 4 days before first dose.

Table 6-3. Schedule of Events for a 4-Week Treatment Group

Assessments \ Interval	Screen -50 to -1	Day 1	Day 2	Day 3	Week 1*	Week 2*	Week 3*	Week 4*
PK Samples [5]		X			X	X	X	X
Hematology [6]	X	X			X	X		X
Serum Chemistries [6]	X	X			X	X		X
Urinalysis	X	X			X	X		X
ALT/AST [6]	X	X			X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X
Pregnancy Test [9]	X							X
Stored serum sample [10]	X	X			X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335 (and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Week 3, 2-4 hours postdose, and at Week 4, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1, 2 and 3.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* Weekly visit may occur ±1 day from the expected visit date.

Table 6-4. Schedule of Events for Post-dosing (Safety and Virology) Follow-up Visits (All Treatment Cohorts)

Post-dosing Follow-up							
			Virology Follow-up Visits (After end of Treatment [2] OR After Time of Treatment Failure [if earlier]) [3]				
Assessment	Early Termination (ET) Visit [1]	Safety Follow-up Visit 4 Weeks (±1 week) After the Last Actual Dose of Study Drug	Week 4 (±1 week) [4]	Week 8 (±1 weeks)	Week 12 (±2 weeks)	Week 18 (±2 weeks)	Week 24 (±2 weeks)
Physical Exam [5]	X	X					
Echocardiogram	X	X					
Vital Signs	X	X					
Triplicate 12 Lead ECG	X	X					
Serum Chemistry w/ ALT & AST	X	X					
Hematology	X	X					
Urinalysis	X	X					
HCV RNA concentration	X	X	X	X	X	X	X
Plasma for drug resistance monitoring	X	X	X	X	X	X	X
AE & Conmed Evaluation	X	X	X	X	X	X	X
PK Samples [6]	X	X	X	X	X	X	X
Pregnancy test[7]	X	X		X	X		X
Stored Serum Sample[8]	X	X					

[1] Subjects who prematurely discontinue from their assigned study treatment should return to the clinic as soon as possible for an Early Termination Visit. If the timing of the Early Termination Visit coincides with the Safety Follow up Visit, then assessments for the Early Termination Visit should be conducted.

[2] For subjects with less than lower limit of quantitation (<LLOQ) HCV RNA at actual end of treatment (EOT) (if prematurely discontinued treatment, discontinuation was for reasons other than on-treatment virologic failure (e.g., AE).

[3] On-treatment failure is defined as virologic failure or breakthrough. No subject will be followed for more than 24 weeks.

[4] Note: The Week 4 Virology Follow up Visit will coincide with the Safety Follow-up Visit for most subjects and may be replaced by the Safety Follow-up Visit in these cases; it will not coincide for subjects who have relapse or for subjects who discontinue early with <LLOQ HCV RNA.

[5] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.

[6] PK sampling will be conducted for ODV at the time of visit.

[7] Heterosexually active women of childbearing potential.

[8] For additional safety investigations as needed.

11.2 Appendix 2 - Criteria for Potentially Clinically Significant Abnormalities (PCSA)

Vital signs		
PR	≤ 50 bpm	≥ 120 bpm
SBP	≤ 90 mmHg	> 140 mmHg
DBP	≤ 50 mmHg	> 90 mmHg
ECG parameters		
PR	<120 ms	> 200 ms
QRS		> 120 ms
QTcB or QTcF		> 450 - ≤ 480 ms > 480 ms > 500 ms change from baseline ≥ 30 - ≤ 60 ms change from baseline > 60 ms

11.3 Appendix 3 - List of tables, listings and figures included in the clinical study report

NUMBER	TITLE
14	**Tables, figures and graphs referred to but not included in the text**
14.1	**Demographic data**
14.1.1	**Description of study subjects**
14.1.1.1	Subjects disposition - Included set
14.1.1.2	Analysis sets – Included set
14.1.2	**Protocol deviations**
14.1.2.1	Deviations relating to inclusion/exclusion criteria - Safety set
14.1.2.2	Other deviations - Safety set
14.1.3	**Demographic data and baseline characteristics**
14.1.3.1.1	Demographic data - Safety set
14.1.3.1.2	Demographic data - PKS
14.1.3.2	**Other baseline characteristics**
14.1.3.2.1.1	HCV genotype – Safety set
14.1.3.2.1.2	HCV genotype – PKS
14.1.3.2.2.1	HCV RNA – Safety set
14.1.3.2.2.2	HCV RNA – PKS
14.1.3.2.3.1	Serology - Safety set
14.1.3.2.3.2	Serology - PKS
14.1.3.2.4	Listing of positive results of serology - Safety set
14.1.3.2.5.1	Cirrhosis status - Safety set
14.1.3.2.5.2	Cirrhosis status - PKS set
14.1.3.2.6.1	Liver biopsy – Safety set

14.1.3.2.6.2	Liver biopsy – PKS
14.1.3.2.7.1	Fibroscan - Safety set
14.1.3.2.7.2	Fibroscan - PKS set
14.1.3.3	**Medical and surgical history**
14.1.3.3.1	Previous medical and surgical history (except liver diseases) - Safety set
14.1.3.3.2	Ongoing medical and surgical history (except liver diseases) - Safety set
14.1.3.3.3	Previous liver diseases - Safety set
14.1.3.3.4	Ongoing liver diseases - Safety set
14.1.3.4	**Previous and concomitant medications**
14.1.3.4.1	Previous medications - Safety set
14.1.3.4.2	Concomitant medications - Safety set
14.2	**Pharmacokinetic data**
14.2.1	**Plasma concentrations**
14.2.1.1	**AL-335, ALS-022399 and ALS-022227**
14.2.1.1.1	Plasma concentrations for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set
14.2.1.1.2	Graphs of plasma concentrations means (±SD) over time for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set
14.2.1.1.2.1	Graphs of plasma concentrations means (±SD) over time for AL-335, ALS-022399 and ALS-022227 by analyte
14.2.1.1.2.2	Graphs of plasma concentrations means (±SD) over time for AL-335, ALS-022399 and ALS-022227 by cohort
14.2.1.1.3	Graphs of trough plasma concentrations means (±SD) over time for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set

14.2.1.2	**Simeprevir**
14.2.1.2.1	Plasma concentrations for simeprevir - Pharmacokinetic set
14.2.1.2.2	Graphs of plasma concentrations means (±SD) over time for simeprevir - Pharmacokinetic set
14.2.1.2.3	Graphs of trough plasma concentrations means (±SD) over time for simeprevir - Pharmacokinetic set
14.2.1.3	**Odalasvir**
14.2.1.3.1	Plasma concentrations for odalasvir - Pharmacokinetic set
14.2.1.3.2	Graphs of plasma concentrations means (±SD) over time for odalasvir - Pharmacokinetic set
14.2.1.3.3	Graphs of trough plasma concentrations means (±SD) over time for odalasvir - Pharmacokinetic set
14.2.2	**PK parameters in plasma**
14.2.2.1	**AL-335, ALS-022399 and ALS-022227**
14.2.2.1.1	PK parameters in plasma for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set
14.2.2.1.2	Scatter plots of C_{max} and $AUC_{0-\tau}$ for AL-335, ALS-022399 and ALS-022227 by cohort - Pharmacokinetic set
14.2.2.1.3	Box whisker plots of C_{max} and $AUC_{0-\tau}$ for AL-335, ALS-022399 and ALS-022227 by cohort - Pharmacokinetic set
14.2.2.2	**Simeprevir**
14.2.2.2.1	PK parameters in plasma for simeprevir - Pharmacokinetic set
14.2.2.2.2	Scatter plots of C_{max} and $AUC_{0-\tau}$ for simeprevir by cohort - Pharmacokinetic set
14.2.2.2.3	Box whisker plots of C_{max} and $AUC_{0-\tau}$ for simeprevir by cohort - Pharmacokinetic set
14.2.2.3	**Odalasvir**

14.2.2.3.1	PK parameters in plasma for odalasvir - Pharmacokinetic set
14.2.2.3.2	Scatter plots of C_{max} and $AUC_{0-\tau}$ for odalasvir by cohort - Pharmacokinetic set
14.2.2.3.3	Box whisker plots of C_{max} and $AUC_{0-\tau}$ for odalasvir by cohort - Pharmacokinetic set
14.3	**Safety data**
14.3.1	**Adverse events**
14.3.1.1	**Adverse events - Safety set**
14.3.1.2	**Treatment emergent adverse events**
14.3.1.2.1	Treatment emergent adverse events summary table - Safety set
14.3.1.2.2	Treatment emergent adverse events - Safety set
14.3.1.2.3	Treatment emergent adverse events by preferred term - Safety set
14.3.1.2.4	Treatment emergent adverse events by intensity - Safety set
14.3.1.2.5	Treatment emergent adverse events by causality - Safety set
14.3.1.2.6	Treatment emergent serious adverse events by preferred term - Safety set
14.3.1.2.7	Treatment emergent adverse events leading to any study drug discontinuation by preferred term - Safety set
14.3.1.2.8	Treatment emergent adverse events of special interest - Safety set
14.3.1.2.9	Adverse Events with fatal outcome – Included set
14.3.1.2.10	The incidence and comparable prevalence rate per 2-week time interval for any AEs
14.3.1.2.11	The incidence rates for adverse events of special interest by WHO toxicity grade
14.3.1.2.12	The incidence rates for adverse events of special interest by relationship to study drugs

14.3.1.2.13	The incidence rates for serious adverse events of special interest by relationship to study drugs
14.3.1.2.14	Time to the first occurrence of adverse events of special interest
14.3.1.2.15	The incidence and comparable prevalence rate per 2-week time interval for adverse events of special interest
14.3.1.3.1	Graph of incidence and comparable prevalence rate for any AE over time
14.3.1.3.2	Kaplan Meier Curve for the Time to Onset of adverse events of special interest
14.3.1.3.3	Graph of incidence and comparable prevalence rate for adverse event of special interest over time
14.3.1.3.4	Bar chart of the worst toxicity grade of cardiac events over time
14.3.2.1	Listing of deaths, SAEs and TEAEs leading to study drug discontinuation - Safety set
14.3.2.2	Listing of TEAEs with grade 3 or grade 4 - Safety set
14.3.2.3	Glossary of adverse events
14.3.2.4	Listing of adverse events for subjects who met the study stopping rules
14.3.3	**Clinical laboratory data**
14.3.3.1	**Haematology**
14.3.3.1.1	Haematology parameters - Safety set
14.3.3.1.2	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – Worst post-baseline value - Safety set
14.3.3.1.3	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – By measurement time - Safety set
14.3.3.1.4	Listing of all values for subjects presenting any treatment emergent value that is grade 3 and 4 (toxicity grading scale) - Safety set
14.3.3.1.5	Listing of subjects with treatment emergent abnormal values -

	Safety set
14.3.3.1.6	Graphs of individual subject values (spaghetti plots) – Safety Set
14.3.3.1.7	Cross-tabulation of the worst toxicity grades versus baseline
14.3.3.1.8	Plot of mean(SE) by cohort over time
14.3.3.1.9	Plot of mean(SE) change from baseline by cohort over time
14.3.3.1.10	Bar chart of the treatment emergent abnormality by toxicity grade over time
14.3.3.2	**Blood chemistry**
14.3.3.2.1	Blood chemistry parameters - Safety set
14.3.3.2.2	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – Worst post-baseline value - Safety set
14.3.3.2.3	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – By measurement time - Safety set
14.3.3.2.4	Listing of all values for subjects presenting any treatment emergent values that are grade 3 and 4 (toxicity grading scale) - Safety set
14.3.3.2.5	Listing of subjects with treatment emergent abnormal values - Safety set
14.3.3.2.6	Graphs of individual subject values (spaghetti plots) – Safety Set
14.3.3.2.7	Cross-tabulation of the worst toxicity grades versus baseline
14.3.3.2.8	Plot of mean(SE) by cohort over time
14.3.3.2.9	Plot of mean(SE) change from baseline by cohort over time
14.3.3.2.10	Bar chart of the treatment emergent abnormality by toxicity grade over time
14.3.3.3	**Coagulation - Safety set**
14.3.3.3.1	Coagulation parameters - Safety set
14.3.3.3.2	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – Worst post-baseline value - Safety set

14.3.3.3.3	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – By measurement time - Safety set
14.3.3.3.4	Listing of all values for subjects presenting any treatment emergent values that are grade 3 and 4 (toxicity grading scale) - Safety set
14.3.3.3.5	Listing of subjects with treatment emergent abnormal values - Safety set
14.3.3.3.6	Cross-tabulation of the worst toxicity grades versus baseline
14.3.3.3.7	Plot of mean(SE) by cohort over time
14.3.3.3.8	Plot of mean(SE) change from baseline by cohort over time
14.3.3.3.9	Bar chart of the treatment emergent abnormality by toxicity grade over time
14.3.3.4	**Urinalysis - Safety set**
14.3.3.4.1	Urinalysis parameters - Safety set
14.3.3.4.2	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – Worst post-baseline value - Safety set
14.3.3.4.3	Number and percentage of subjects by treatment emergent toxicity grade (Grade 1,2,3,4,3+4) – By measurement time - Safety set
14.3.3.4.4	Listing of all values for subjects presenting any treatment emergent values that are grade 3 and 4 (toxicity grading scale) - Safety set
14.3.3.4.5	Listing of subjects with treatment emergent abnormal values - Safety set
14.3.4	**Other safety parameters**
14.3.4.1	**Vital signs data**
14.3.4.1.1	Vital signs parameters - Safety set
14.3.4.1.2	Number and percentage of subjects presenting PCSA values - Safety set
14.3.4.1.3	Listing of subjects presenting PCSA values - Safety set

14.3.4.1.4	Number and percentage of subjects presenting abnormal values – Worst post-baseline value - Safety set
14.3.4.1.5	Number and percentage of subjects presenting abnormal values – By measurement time - Safety set
14.3.4.1.6	Listing of subjects presenting abnormal values - Safety set
14.3.4.1.7	Plots of mean (SE) by cohort over time
14.3.4.2	**Electrocardiogram data**
14.3.4.2.1	ECG parameters – Safety set
14.3.4.2.2	Number and percentage of subjects with PCSA values - Safety set
14.3.4.2.3	Listing of subjects presenting PCSA values - Safety set
14.3.4.2.4	Listing of All ECG Parameters over time for Subjects with Any Post-baseline Overall Statement of Potentially Clinically Significant Abnormal ECG
14.3.4.2.5	Listing of Subjects with Potentially Progressive PR Prolongation
14.3.4.2.6	Number and percentage of subjects presenting abnormal values – Worst post-baseline value - Safety set
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14.3.4.2.8	Listing of subjects presenting abnormal values - Safety set
14.3.4.2.9	Graphs of individual subject values (spaghetti plots) – Safety Set
14.3.4.2.10	Cross-Tabulation of the worst ECG abnormalities in actual value versus the baseline value
14.3.4.2.11	Cross-Tabulation of the worst QTc increase versus the abnormality on the actual value
14.3.4.2.12	Plots of actual mean(SE) by cohort over time
14.3.4.2.13	Plots of mean change from baseline(SE) by cohort over time
14.3.4.2.14	Spaghetti plot of PR for the patients who had prolonged PR interval

	or AV block (grade>=1)
14.3.4.3	**Echocardiogram data**
14.3.4.3.1	Summary Table of Maximum Decrease from baseline in Mean Ejection Fraction – Safety set
14.3.4.3.2	Number and Percentage of subjects who have a decrease greater than 5% or ≤10% and >10% compared to baseline – Safety set
14.3.4.3.3	Listing of all EF values for Subjects with any >5%-≤10 Decrease from baseline in Mean Ejection Fraction – Safety set
14.3.4.3.4	Listing of all EF values for Subjects with any More Than 10% Decrease from baseline in Mean Ejection Fraction – Safety set
14.3.4.3.5	Listing of Ejection Fraction Data and Overall Comment – Safety set
14.3.4.3.6	Echocardiogram parameters – Safety set
14.3.4.3.7	Number and percentage of subjects with abnormal values - Safety set
14.3.4.3.8	Graphs of individual subject values (spaghetti plots) – Safety set
14.3.4.3.9	Plots of actual mean(SE) by cohort over time
14.3.4.3.10	Plots of mean change from baseline(SE) by cohort over time
14.3.4.4	Weight and BMI – Safety set
14.3.4.5	**Physical examination**
14.3.4.5.1	Physical examination - Safety set
14.3.4.5.2	Abnormal physical examination - Safety set
14.3.4.6	Positive pregnancy test - Safety set
14.4	**Efficacy data**
14.4.1	HCV RNA – Safety set
14.4.2	Number and percentage of subjects who are HCV RNA not detected or below the limit of quantification – Safety set

14.4.3	**Sustained virologic response**
14.4.3.1	Number and percentage of subjects with sustained virologic response 12 weeks after end of treatment – Safety set
14.4.3.2	Number and percentage of subjects with sustained virologic response 4 weeks after end of treatment – Safety set
14.4.3.3	Number and percentage of subjects with sustained virologic response 24 weeks after end of treatment – Safety set
14.4.4	Number and percentage of subjects with virologic failure – Safety set
14.4.5.1	Graphs of individual subject values of viral load (spaghetti plots) – Safety set
14.4.5.2	Graphs of mean viral load change from baseline – Safety set
16.2	**SUBJECT DATA LISTINGS**
16.2.1	**Subjects disposition**
16.2.1.1	Discontinued subjects - Included set
16.2.1.2	Subjects disposition and analysis sets - Included set
16.2.1.3	End of study status - Included set
16.2.1.4	Subject visit dates - Included set
16.2.2	**Protocol deviations**
16.2.2.1	Deviations relating to inclusion/exclusion criteria - Safety set
16.2.2.2	Other deviations – Safety set
16.2.3	**Subjects excluded from analysis sets - Included set**
16.2.4	**Demographic data and baseline characteristics**
16.2.4.1	**Demographic data and baseline characteristics - Safety set**
16.2.4.2	**Other baseline characteristics**
16.2.4.2.1	HCV genotype – Safety set

16.2.4.2.2	HCV RNA – Safety set
16.2.4.2.3	Serology - Safety set
16.2.4.2.4	Childbearing status – Safety set
16.2.4.2.5	Contraception method – Safety set
16.2.4.2.6	Alcohol consumption – Safety set
16.2.4.2.7	Cirrhosis status – Safety set
16.2.4.2.8	Liver biopsy – Safety set
16.2.4.2.9	Fibroscan – Safety set
16.2.4.2.10	Child-Pugh class assessment (only for compensated cirrhosis cohort) – Safety set
16.2.4.2.11	Hepatocellular carcinoma assessment (only for compensated cirrhosis cohorts) – Safety set
16.2.4.3	**Medical and surgical history**
16.2.4.3.1	Medical and surgical history (except liver diseases) – Safety set
16.2.4.3.2	Liver diseases – Safety set
16.2.4.4	**Previous and concomitant medications**
16.2.4.4.1	Previous medications - Safety set
16.2.4.4.2	Concomitant medications - Safety set
16.2.5	**Compliance and/or drug concentration data**
16.2.5.1	**Compliance and dosing data**
16.2.5.1.1	IMP administration – Safety set
16.2.5.1.2	Meals intake – Safety set
16.2.5.2	**Pharmacokinetic data**
16.2.5.2.1	**Plasma pharmacokinetic concentrations and parameters**
16.2.5.2.1.1	**AL-335, ALS-022399 and ALS-022227**

16.2.5.2.1.1.1	Plasma concentrations for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set
16.2.5.2.1.1.2	Plasma concentrations for AL-335, ALS-022399 and ALS-022227 – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event - Pharmacokinetic set
16.2.5.2.1.1.3	Individual plasma concentration time curves for AL-335, ALS-022399 and ALS-022227- Pharmacokinetic set
16.2.5.2.1.1.4	PK parameters in plasma for AL-335, ALS-022399 and ALS-022227 - Pharmacokinetic set
16.2.5.2.1.1.5	PK parameters in plasma for AL-335, ALS-022399 and ALS-022227 – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event – Pharmacokinetic set
16.2.5.2.1.2	**Simeprevir**
16.2.5.2.1.2.1	Plasma concentrations for Simeprevir - Pharmacokinetic set
16.2.5.2.1.2.2	Plasma concentrations for Simeprevir – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event - Pharmacokinetic set
16.2.5.2.1.2.3	Individual plasma concentration time curves for Simeprevir - Pharmacokinetic set
16.2.5.2.1.2.4	PK parameters in plasma for Simeprevir - Pharmacokinetic set
16.2.5.2.1.2.5	PK parameters in plasma for Simeprevir – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event - Pharmacokinetic set
16.2.5.2.1.3	**Odalasvir**
16.2.5.2.1.3.1	Plasma concentrations for Odalasvir - Pharmacokinetic set
16.2.5.2.1.3.2	Plasma concentrations for Odalasvir – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event - Pharmacokinetic set

16.2.5.2.1.3.3	Individual plasma concentration time curves for Odalasvir - Pharmacokinetic set
16.2.5.2.1.3.4	PK parameters in plasma for Odalasvir - Pharmacokinetic set
16.2.5.2.1.3.5	PK parameters in plasma for Odalasvir – Subgroup of subjects who discontinue the study for an adverse event, experience a severe adverse event or a serious adverse event - Pharmacokinetic set
16.2.6	**Efficacy data**
16.2.6.1	HCV RNA – Safety set
16.2.6.2	HCV RNA for subjects with virologic failures– Safety set
16.2.7	**Adverse event listings**
16.2.7.1	All adverse events – Included set
16.2.7.2	Treatment emergent adverse events - Safety set
16.2.7.3	Serious adverse events – Included set
16.2.7.4	Treatment emergent adverse events leading to study drug discontinuation – Safety set
16.2.7.5	Treatment emergent adverse events of special interest - Safety set
16.2.7.6	Adverse events with fatal outcome – Included set
16.2.7.7	**Rash assessments**
16.2.7.7.1	Photosensitivity – Safety set
16.2.7.7.2	Rash assessments – Safety set
16.2.7.7.3	Associated rash or cutaneous event – Safety set
16.2.7.7.4	Rash or cutaneous event follow-up – Safety set
16.2.7.7.5	Final rash, cutaneous event or photosensitivity evaluation – Safety set
16.2.7.7.6	Primary lesions of rash or cutaneous event – Safety set
16.2.7.7.7	Secondary lesions of rash or cutaneous event – Safety set

16.2.7.7.8	Rash questionnaire – Safety set
16.2.7.7.9	Rash event grading – Safety set
16.2.8	**Clinical laboratory data**
16.2.8.1	**Haematology**
16.2.8.1.1	Normal ranges for SI units and local units
16.2.8.1.2	All haematology values (SI unit) - Safety set
16.2.8.2	**Blood chemistry**
16.2.8.2.1	Normal ranges for SI units and local units
16.2.8.2.2	All blood chemistry values (SI unit) - Safety set
16.2.8.3	**Coagulation**
16.2.8.3.1	Normal ranges for SI units and local units
16.2.8.3.2	All coagulation values (SI unit) - Safety set
16.2.8.4	**Urinalysis**
16.2.8.4.1	Normal ranges for SI units and local units
16.2.8.4.2	All urinalysis values (SI unit) - Safety set
16.2.8.5	Hormonology – Safety set
16.2.9	**Other safety parameters**
16.2.9.1	**Vital signs data**
16.2.9.1.1	PCSA ranges
16.2.9.1.2	Vital signs parameters - Safety set
16.2.9.2	**Electrocardiogram data**
16.2.9.2.1	PCSA ranges
16.2.9.2.2.1	Standard 12-lead ECG parameters (centrally read data) - Safety set

16.2.9.3	**Echocardiogram data – Safety set**
16.2.9.4	**Weight and BMI – Safety set**
16.2.9.5	**Physical examination – Safety set**
16.2.9.6	**Pregnancy test - Safety set**
16.2.9.7	**Toxicology – Safety set**

11.4 Appendix 4: Events of special/clinical interest

11.4.1 Search terms for Events of Special/Clinical Interest

	MedrDRA Term Level	Searching Terms
Events of special interest		
Cardiac Events	SMQ	Cardiac arrhythmias (SMQ) [Arrhythmia related investigations, signs and symptoms (SMQ); Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)]; Cardiac failure (SMQ); Cardiomyopathy (SMQ); Ischaemic heart disease (SMQ)[Myocardial infarction (SMQ)]; Shock (SMQ)[Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)]; Torsade de pointes/QT prolongation (SMQ); Please see Appendix 3
Increased Bilirubin	MedDRA PTs	Bilirubin conjugated abnormal Bilirubin conjugated increased Bilirubin excretion disorder Bilirubinuria Blood bilirubin abnormal Blood bilirubin increased Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice cholestatic Jaundice extrahepatic obstructive Jaundice hepatocellular Ocular icterus Urine bilirubin increased Yellow skin
Events of clinical interest		
Rash (all type)	MedDRA HLTs, PTs	Erythemas - HLT Papulosquamous conditions - HLT Rashes, eruptions and exanthems NEC - HLT PT: Photodermatosis

		Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn
	SMQ	SMQ-Severe cutaneous adverse reaction: All narrow terms and selected broad terms (refer APPENDIX 2B below)
Pruritus	MedDRA HLT	Pruritus NEC
Photosensitivity conditions	MedDRA PTs	Photodermatosis Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn

11.4.2 RASH – SMQ19.1

SMQ 19.1: "Severe cutaneous adverse reaction" : all narrow and selected broad terms

SCOPE	Preferred Term
NARROW	CUTANEOUS VASCULITIS
NARROW	DERMATITIS BULLOUS
NARROW	DERMATITIS EXFOLIATIVE
NARROW	DERMATITIS EXFOLIATIVE GENERALISED
NARROW	ERYTHEMA MULTIFORME
NARROW	OCULOMUCOCUTANEOUS SYNDROME
NARROW	SKIN NECROSIS
NARROW	STEVENS-JOHNSON SYNDROME
NARROW	TOXIC EPIDERMAL NECROLYSIS
NARROW	ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS
NARROW	TOXIC SKIN ERUPTION
NARROW	EPIDERMAL NECROSIS
NARROW	EXFOLIATIVE RASH
NARROW	DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS
BROAD	BLISTER
BROAD	BULLOUS IMPETIGO
BROAD	DRUG ERUPTION
BROAD	EPIDERMOLYSIS BULLOSA
BROAD	MUCOCUTANEOUS ULCERATION
BROAD	NIKOLSKY'S SIGN
BROAD	PEMPHIGOID
BROAD	PEMPHIGUS
BROAD	SKIN EROSION
BROAD	SKIN EXFOLIATION
BROAD	EPIDERMOLYSIS
BROAD	ACQUIRED EPIDERMOLYSIS BULLOSA

11.4.3 CARDIAC EVENTS - SMQ19.1

				Narrow/Broad	PT Term
Cardiac arrhythmias (SMQ)					
	Arrhythmia related investigations, signs and symptoms (SMQ)				
				Narrow	Chronotropic incompetence
				Narrow	Electrocardiogram repolarisation abnormality
				Narrow	Electrocardiogram RR interval prolonged
				Narrow	Electrocardiogram U-wave abnormality
				Narrow	Sudden cardiac death
				Broad	Bezold-Jarisch reflex
				Broad	Bradycardia
				Broad	Cardiac arrest
				Broad	Cardiac death
				Broad	Cardiac telemetry abnormal
				Broad	Cardio-respiratory arrest
				Broad	Central bradycardia
				Broad	Electrocardiogram abnormal
				Broad	Electrocardiogram ambulatory abnormal
				Broad	Electrocardiogram change
				Broad	Heart rate abnormal
				Broad	Heart rate decreased
				Broad	Heart rate increased
				Broad	Loss of consciousness
				Broad	Palpitations
				Broad	Rebound tachycardia
				Broad	Sudden death
				Broad	Syncope
				Broad	Tachycardia
				Broad	Tachycardia paroxysmal
	Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)				
		Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)			
			Bradyarrhythmia terms, nonspecific (SMQ)		
				Narrow	Bradyarrhythmia
				Narrow	Ventricular asystole
			Conduction defects (SMQ)		
				Narrow	Accessory cardiac pathway
				Narrow	Adams-Stokes syndrome
				Narrow	Agonal rhythm

				Narrow	Atrial conduction time prolongation
				Narrow	Atrioventricular block
				Narrow	Atrioventricular block complete
				Narrow	Atrioventricular block first degree
				Narrow	Atrioventricular block second degree
				Narrow	Atrioventricular conduction time shortened
				Narrow	Atrioventricular dissociation
				Narrow	Bifascicular block
				Narrow	Brugada syndrome
				Narrow	Bundle branch block
				Narrow	Bundle branch block bilateral
				Narrow	Bundle branch block left
				Narrow	Bundle branch block right
				Narrow	Conduction disorder
				Narrow	Defect conduction intraventricular
				Narrow	Electrocardiogram delta waves abnormal
				Narrow	Electrocardiogram PQ interval prolonged
				Narrow	Electrocardiogram PQ interval shortened
				Narrow	Electrocardiogram PR prolongation
				Narrow	Electrocardiogram PR shortened
				Narrow	Electrocardiogram QRS complex prolonged
				Narrow	Electrocardiogram QT prolonged
				Narrow	Electrocardiogram repolarisation abnormality
				Narrow	Lenegre's disease
				Narrow	Long QT syndrome
				Narrow	Paroxysmal atrioventricular block
				Narrow	Sinoatrial block
				Narrow	Trifascicular block
				Narrow	Ventricular dyssynchrony
				Narrow	Wolff-Parkinson-White syndrome
			Disorders of sinus node function (SMQ)		
				Narrow	Nodal arrhythmia
				Narrow	Nodal rhythm
				Narrow	Sinus arrest
				Narrow	Sinus arrhythmia
				Narrow	Sinus bradycardia
				Narrow	Sinus node dysfunction
				Narrow	Wandering pacemaker
		Cardiac arrhythmia terms, nonspecific (SMQ)			
				Narrow	Arrhythmia

				Narrow	Heart alternation
				Narrow	Heart rate irregular
				Narrow	Pacemaker generated arrhythmia
				Narrow	Pacemaker syndrome
				Narrow	Paroxysmal arrhythmia
				Narrow	Pulseless electrical activity
				Narrow	Reperfusion arrhythmia
				Narrow	Withdrawal arrhythmia
		Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)			
			Supraventricular tachyarrhythmias (SMQ)		
				Narrow	Arrhythmia supraventricular
				Narrow	Atrial fibrillation
				Narrow	Atrial flutter
				Narrow	Atrial parasystole
				Narrow	Atrial tachycardia
				Narrow	Junctional ectopic tachycardia
				Narrow	Sinus tachycardia
				Narrow	Supraventricular extrasystoles
				Narrow	Supraventricular tachyarrhythmia
				Narrow	Supraventricular tachycardia
				Broad	ECG P wave inverted
				Broad	Electrocardiogram P wave abnormal
				Broad	Retrograde p-waves
			Tachyarrhythmia terms, nonspecific (SMQ)		
				Narrow	Anomalous atrioventricular excitation
				Narrow	Cardiac fibrillation
				Narrow	Cardiac flutter
				Narrow	Extrasystoles
				Narrow	Tachyarrhythmia
			Ventricular tachyarrhythmias (SMQ)		
				Narrow	Accelerated idioventricular rhythm
				Narrow	Cardiac fibrillation
				Narrow	Parasystole
				Narrow	Rhythm idioventricular
				Narrow	Torsade de pointes
				Narrow	Ventricular arrhythmia
				Narrow	Ventricular extrasystoles
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter

				Narrow	Ventricular parasystole
				Narrow	Ventricular pre-excitation
				Narrow	Ventricular tachyarrhythmia
				Narrow	Ventricular tachycardia
Cardiac failure (SMQ)					
				Narrow	Acute left ventricular failure
				Narrow	Acute pulmonary oedema
				Narrow	Acute right ventricular failure
				Narrow	Cardiac asthma
				Narrow	Cardiac failure
				Narrow	Cardiac failure acute
				Narrow	Cardiac failure chronic
				Narrow	Cardiac failure congestive
				Narrow	Cardiac failure high output
				Narrow	Cardiogenic shock
				Narrow	Cardiopulmonary failure
				Narrow	Cardiorenal syndrome
				Narrow	Chronic left ventricular failure
				Narrow	Chronic right ventricular failure
				Narrow	Cor pulmonale
				Narrow	Cor pulmonale acute
				Narrow	Cor pulmonale chronic
				Narrow	Ejection fraction decreased
				Narrow	Hepatic congestion
				Narrow	Hepatojugular reflux
				Narrow	Left ventricular failure
				Narrow	Low cardiac output syndrome
				Narrow	Neonatal cardiac failure
				Narrow	Obstructive shock
				Narrow	Pulmonary oedema
				Narrow	Pulmonary oedema neonatal
				Narrow	Radiation associated cardiac failure
				Narrow	Right ventricular ejection fraction decreased
				Narrow	Right ventricular failure
				Narrow	Ventricular failure
				Broad	Artificial heart implant
				Broad	Atrial natriuretic peptide abnormal
				Broad	Atrial natriuretic peptide increased
				Broad	Bendopnoea
				Broad	Brain natriuretic peptide abnormal

				Broad	Brain natriuretic peptide increased
				Broad	Cardiac cirrhosis
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac index decreased
				Broad	Cardiac output decreased
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardio-respiratory distress
				Broad	Cardiothoracic ratio increased
				Broad	Central venous pressure increased
				Broad	Diastolic dysfunction
				Broad	Dilatation ventricular
				Broad	Dyspnoea paroxysmal nocturnal
				Broad	Heart transplant
				Broad	Hepatic vein dilatation
				Broad	Jugular vein distension
				Broad	Left ventricular dilatation
				Broad	Left ventricular dysfunction
				Broad	Left ventricular enlargement
				Broad	Lower respiratory tract congestion
				Broad	Myocardial depression
				Broad	Nocturnal dyspnoea
				Broad	N-terminal prohormone brain natriuretic peptide abnormal
				Broad	N-terminal prohormone brain natriuretic peptide increased
				Broad	Oedema
				Broad	Oedema due to cardiac disease
				Broad	Oedema neonatal
				Broad	Oedema peripheral
				Broad	Orthopnoea
				Broad	Peripheral oedema neonatal
				Broad	Peripheral swelling
				Broad	Post cardiac arrest syndrome
				Broad	Prohormone brain natriuretic peptide abnormal
				Broad	Prohormone brain natriuretic peptide increased
				Broad	Pulmonary congestion

				Broad	Right ventricular dilatation
				Broad	Right ventricular dysfunction
				Broad	Right ventricular enlargement
				Broad	Scan myocardial perfusion abnormal
				Broad	Stroke volume decreased
				Broad	Surgical ventricular restoration
				Broad	Systolic dysfunction
				Broad	Venous pressure increased
				Broad	Venous pressure jugular abnormal
				Broad	Venous pressure jugular increased
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyssynchrony
Cardiomyopathy (SMQ)					
				Narrow	Atrial septal defect acquired
				Narrow	Biopsy heart abnormal
				Narrow	Cardiac amyloidosis
				Narrow	Cardiac hypertrophy
				Narrow	Cardiac sarcoidosis
				Narrow	Cardiac septal hypertrophy
				Narrow	Cardiac siderosis
				Narrow	Cardiomyopathy
				Narrow	Cardiomyopathy acute
				Narrow	Cardiomyopathy alcoholic
				Narrow	Cardiomyopathy neonatal
				Narrow	Cardiotoxicity
				Narrow	Congestive cardiomyopathy
				Narrow	Cytotoxic cardiomyopathy
				Narrow	Diabetic cardiomyopathy
				Narrow	Ejection fraction abnormal
				Narrow	Ejection fraction decreased
				Narrow	Eosinophilic myocarditis
				Narrow	HIV cardiomyopathy
				Narrow	Hypertensive cardiomyopathy
				Narrow	Hypertrophic cardiomyopathy
				Narrow	Ischaemic cardiomyopathy
				Narrow	Metabolic cardiomyopathy
				Narrow	Myocardial calcification
				Narrow	Myocardial fibrosis
				Narrow	Myocardial haemorrhage

				Narrow	Non-obstructive cardiomyopathy
				Narrow	Peripartum cardiomyopathy
				Narrow	Pulmonary arterial wedge pressure increased
				Narrow	Restrictive cardiomyopathy
				Narrow	Right ventricular ejection fraction decreased
				Narrow	Stress cardiomyopathy
				Narrow	Tachycardia induced cardiomyopathy
				Narrow	Thyrotoxic cardiomyopathy
				Narrow	Ventricular septal defect acquired
				Narrow	Viral cardiomyopathy
				Broad	Abnormal precordial movement
				Broad	Acquired cardiac septal defect
				Broad	Acute left ventricular failure
				Broad	Alcohol septal ablation
				Broad	Allergic myocarditis
				Broad	Arrhythmia
				Broad	Arrhythmia supraventricular
				Broad	Artificial heart implant
				Broad	Ascites
				Broad	Atrial hypertrophy
				Broad	Atrial pressure increased
				Broad	Autoimmune myocarditis
				Broad	Bendopnoea
				Broad	Blood pressure diastolic abnormal
				Broad	Blood pressure diastolic decreased
				Broad	Blood pressure diastolic increased
				Broad	Blood pressure fluctuation
				Broad	Blood pressure inadequately controlled
				Broad	Blood pressure systolic abnormal
				Broad	Blood pressure systolic decreased
				Broad	Blood pressure systolic increased
				Broad	Cardiac aneurysm
				Broad	Cardiac arrest
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac electrophysiologic study abnormal
				Broad	Cardiac failure
				Broad	Cardiac failure acute
				Broad	Cardiac failure chronic
				Broad	Cardiac failure congestive
				Broad	Cardiac function test abnormal

				Broad	Cardiac imaging procedure abnormal
				Broad	Cardiac index abnormal
				Broad	Cardiac index decreased
				Broad	Cardiac index increased
				Broad	Cardiac monitoring abnormal
				Broad	Cardiac operation
				Broad	Cardiac output decreased
				Broad	Cardiac pseudoaneurysm
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventricular scarring
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardiothoracic ratio increased
				Broad	Cardiovascular disorder
				Broad	Cardiovascular function test abnormal
				Broad	Chest pain
				Broad	Chest X-ray abnormal
				Broad	Computerised tomogram thorax abnormal
				Broad	Coxsackie carditis
				Broad	Coxsackie myocarditis
				Broad	Cytomegalovirus myocarditis
				Broad	Decreased ventricular preload
				Broad	Diastolic dysfunction
				Broad	Dilatation atrial
				Broad	Dilatation ventricular
				Broad	Directional Doppler flow tests abnormal
				Broad	Dyspnoea
				Broad	ECG signs of ventricular hypertrophy
				Broad	Echocardiogram abnormal
				Broad	Electrocardiogram abnormal
				Broad	Electrocardiogram change
				Broad	Endocardial fibroelastosis
				Broad	External counterpulsation
				Broad	Gonococcal heart disease
				Broad	Heart and lung transplant
				Broad	Heart transplant
				Broad	Hepatomegaly
				Broad	Hyperdynamic left ventricle

				Broad	Increased ventricular preload
				Broad	Irregular breathing
				Broad	Labile blood pressure
				Broad	Left atrial dilatation
				Broad	Left atrial enlargement
				Broad	Left ventricular dilatation
				Broad	Left ventricular end-diastolic pressure decreased
				Broad	Left ventricular enlargement
				Broad	Left ventricular failure
				Broad	Left ventricular heave
				Broad	Lupus myocarditis
				Broad	Lyme carditis
				Broad	Malarial myocarditis
				Broad	Mental status changes
				Broad	Multiple gated acquisition scan abnormal
				Broad	Myocardiac abscess
				Broad	Myocardial necrosis marker increased
				Broad	Myocarditis
				Broad	Myocarditis bacterial
				Broad	Myocarditis helminthic
				Broad	Myocarditis infectious
				Broad	Myocarditis meningococcal
				Broad	Myocarditis mycotic
				Broad	Myocarditis post infection
				Broad	Myocarditis septic
				Broad	Myocarditis syphilitic
				Broad	Myocarditis toxoplasmal
				Broad	Myoglobinaemia
				Broad	Myoglobinuria
				Broad	Nocturia
				Broad	Nuclear magnetic resonance imaging thoracic abnormal
				Broad	Oedema
				Broad	Orthostatic hypotension
				Broad	Palpitations
				Broad	Papillary muscle disorder
				Broad	Papillary muscle haemorrhage
				Broad	Radiation myocarditis
				Broad	Right atrial dilatation

				Broad	Right atrial enlargement
				Broad	Right atrial pressure increased
				Broad	Right ventricle outflow tract obstruction
				Broad	Right ventricular dilatation
				Broad	Right ventricular enlargement
				Broad	Right ventricular heave
				Broad	Right ventricular systolic pressure decreased
				Broad	Scan myocardial perfusion abnormal
				Broad	Sudden cardiac death
				Broad	Sudden death
				Broad	Surgical ventricular restoration
				Broad	Syncope
				Broad	Systolic anterior motion of mitral valve
				Broad	Systolic dysfunction
				Broad	Ultrasound Doppler abnormal
				Broad	Vascular resistance pulmonary increased
				Broad	Ventricular arrhythmia
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyskinesia
				Broad	Ventricular dyssynchrony
				Broad	Ventricular hyperkinesia
				Broad	Ventricular hypertrophy
				Broad	Ventricular hypokinesia
				Broad	Ventricular remodelling
				Broad	Viral myocarditis
Ischaemic heart disease (SMQ)					
	Myocardial infarction (SMQ)				
				Narrow	Acute coronary syndrome
				Narrow	Acute myocardial infarction
				Narrow	Angina unstable
				Narrow	Blood creatine phosphokinase MB abnormal
				Narrow	Blood creatine phosphokinase MB increased
				Narrow	Coronary artery embolism
				Narrow	Coronary artery occlusion
				Narrow	Coronary artery reocclusion
				Narrow	Coronary artery thrombosis
				Narrow	Coronary bypass thrombosis
				Narrow	Coronary vascular graft occlusion
				Narrow	Kounis syndrome

				Narrow	Myocardial infarction
				Narrow	Myocardial necrosis
				Narrow	Myocardial reperfusion injury
				Narrow	Myocardial stunning
				Narrow	Papillary muscle infarction
				Narrow	Post procedural myocardial infarction
				Narrow	Postinfarction angina
				Narrow	Silent myocardial infarction
				Narrow	Troponin I increased
				Narrow	Troponin increased
				Narrow	Troponin T increased
				Broad	Blood creatine phosphokinase abnormal
				Broad	Blood creatine phosphokinase increased
				Broad	Cardiac ventricular scarring
				Broad	ECG electrically inactive area
				Broad	ECG signs of myocardial infarction
				Broad	Electrocardiogram Q wave abnormal
				Broad	Electrocardiogram ST segment abnormal
				Broad	Electrocardiogram ST segment elevation
				Broad	Electrocardiogram ST-T segment elevation
				Broad	Infarction
				Broad	Myocardial necrosis marker increased
				Broad	Scan myocardial perfusion abnormal
				Broad	Vascular graft occlusion
				Broad	Vascular stent occlusion
				Broad	Vascular stent thrombosis
Shock (SMQ)					
	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)				
				Narrow	Acute left ventricular failure
				Narrow	Adams-Stokes syndrome
				Narrow	Atrial parasystole
				Narrow	Cardiac arrest
				Narrow	Cardiac arrest neonatal
				Narrow	Cardiac death
				Narrow	Cardiac fibrillation
				Narrow	Cardiac flutter
				Narrow	Cardiogenic shock
				Narrow	Cardio-respiratory arrest
				Narrow	Cardio-respiratory arrest neonatal

				Narrow	Cardiovascular insufficiency
				Narrow	Circulatory collapse
				Narrow	Obstructive shock
				Narrow	Pulse absent
				Narrow	Pulseless electrical activity
				Narrow	Shock
				Narrow	Shock symptom
				Narrow	Sudden cardiac death
				Narrow	Ventricular asystole
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter
				Narrow	Ventricular parasystole
				Broad	Acute kidney injury
				Broad	Acute prerenal failure
				Broad	Acute respiratory failure
				Broad	Anuria
				Broad	Blood pressure immeasurable
				Broad	Cerebral hypoperfusion
				Broad	Grey syndrome neonatal
				Broad	Hepatic congestion
				Broad	Hepatojugular reflux
				Broad	Hepatorenal failure
				Broad	Hypoperfusion
				Broad	Jugular vein distension
				Broad	Myocardial depression
				Broad	Neonatal anuria
				Broad	Neonatal multi-organ failure
				Broad	Neonatal respiratory failure
				Broad	Organ failure
				Broad	Prerenal failure
				Broad	Propofol infusion syndrome
				Broad	Renal failure
				Broad	Renal failure neonatal
				Broad	Respiratory failure
Torsade de pointes/QT prolongation (SMQ)					
				Narrow	Electrocardiogram QT interval abnormal
				Narrow	Electrocardiogram QT prolonged
				Narrow	Long QT syndrome
				Narrow	Long QT syndrome congenital
				Narrow	Torsade de pointes

				Narrow	Ventricular tachycardia
				Broad	Cardiac arrest
				Broad	Cardiac death
				Broad	Cardiac fibrillation
				Broad	Cardio-respiratory arrest
				Broad	Electrocardiogram repolarisation abnormality
				Broad	Electrocardiogram U-wave abnormality
				Broad	Loss of consciousness
				Broad	Sudden cardiac death
				Broad	Sudden death
				Broad	Syncope
				Broad	Ventricular arrhythmia
				Broad	Ventricular fibrillation
				Broad	Ventricular flutter
				Broad	Ventricular tachyarrhythmia