Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia

AMG 427

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Investigator's Agreement

I have read the attached protocol amendment entitled "A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia," dated **16 March 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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

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

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia

Study Phase: 1

Indication: Acute Myeloid Leukemia (AML)

Primary Objectives:

- Evaluate the safety and tolerability of AMG 427 in adult subjects with relapsed/refractory (R/R) AML or minimal/measurable residual disease-positive (MRD+) AML
- Estimate the maximum tolerated dose (MTD) and/or a biologically optimal dose (eg, recommended phase 2 dose [RP2D])
- Evaluate the safety and tolerability of extended intravenous (eIV) **administration of** AMG 427

Secondary Objectives:

- Characterize the pharmacokinetics (PK) of AMG 427
- Evaluate the anti-leukemia activity of AMG 427

Exploratory Objectives:

[redacted]

Hypotheses: AMG 427 will demonstrate evidence of anti-leukemic activity at a safe and well tolerated dose in subjects with MRD+ or R/R AML.

Primary Endpoints:

- Safety:
  - Dose limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs)

Secondary Endpoints:

- AMG 427 PK parameters including, but not limited to, maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC), and if feasible, half-life ($t_{½}$) of AMG 427
- Efficacy parameters for (R/R) AML: subject response to treatment with AMG 427 (response defined as complete response/remission [CR]/complete response/remission with incomplete recovery of peripheral blood counts [CRi]/morphologic leukemia-free state, partial remission [per modified International Working Group (IWG) criteria], complete response/remission with partial hematologic recovery [CRh]), and duration of response (duration of response will only be measured for subjects in the expansion cohort)
- Efficacy parameters for MRD+ AML: subject response to treatment with AMG 427 (response refers to conversion from MRD+ status to MRD- status), relapse free survival, and overall

survival (relapse free survival, and overall survival will only be measured for subjects in expansion cohort)

Exploratory Endpoints:

[redacted]

Study Design:

This is a first-in-human (FIH), open-label, phase 1 dose escalation study. AMG 427 will be administered as a short intravenous (IV) infusion (eIV infusion may apply) in adult subjects with MRD+ or R/R AML. The study will be conducted at approximately 15 sites in the United States (US), Australia, Canada, Japan, South Korea, and Germany. Additional countries or sites may be added if necessary.

The dose-escalation cohorts will determine the MTD, safety, tolerability, PK, and PD of AMG 427. Planned dose levels (dose per infusion) the dose escalation cohorts are as follows: [redacted] µg. The starting dose for the [redacted] cohort will be [redacted] µg administered as short term IV infusions on day 1 (D1) and day 5 (D5). The doses administered for the cohorts following cohort [redacted] will be recommended by the Dose Level Review Team (DLRT). The initial several cohorts will receive 2-3 doses (1 each on D1, D3 [if applicable], and D5, and D8 [if applicable]). After reviewing the emerging PK, safety and efficacy data, the DLRT may recommend the administration of additional doses on D3 and D8, to comprise a 2-week cycle with doses on D1/D3/D5/D8. The study will consist of **3** groups:

- **FIH Group:** AMG 427 **administered as** short term IV infusions in R/R AML subjects.
  - **(CLOSED)** Etanercept (Enbrel®) substudy: Etanercept will be administered for CRS prophylaxis 2 days prior to each cycle of AMG 427 short term IV infusions in R/R AML subjects in the US. (Etanercept may be implemented to FIH expansion groups based on emerging data).
- **eIV Infusion Group:** AMG 427 eIV infusions administered on days 1 **and** 2, and 3, with short term IV infusions on day**s** 5 and 8 in R/R AML subjects. (eIV infusion may be implemented to FIH expansion groups based on emerging data).
- **MRD+ Group:** AMG 427 administered in short term IV infusions in MRD+ AML subjects.

The study will have 3 alternative dosing schedules.

- **(CLOSED)** Schedule A
  - D1/D5 or D1/D5/D12/D19 (dexamethasone prophylaxis)
- **(CLOSED)** Schedule B: Etanercept Substudy (R/R AML)
  - D1/D5 or D1/D5/D12/D19 (etanercept 2 days prior to each cycle)

    Etanercept substudy use**d** etanercept 2 days prior to infusion of each cycle D1, and if applicable, 2 days prior to infusion on D12. [redacted]
- Schedule C (Table 16 through Table 21): FIH, eIV (R/R AML)**;** MRD+ Group (MRD+ AML)

- D1/D3/D5/D8 or D1/D3/D5/D8/D12/D19 (dexamethasone prophylaxis)

Note:

- The MRD+ group will use Schedule C for all cycle collections and Table 22 for additional whole blood MRD collection, or Table 23, **as applicable.**

After reviewing additional PK, safety, and efficacy data, the DLRT may recommend the administration of additional doses on day 12 and 19, to comprise a 4-week cycle with doses on either D1/D5/D12/D19 or D1/D3/D5/D8/D12/D19. Once the DLRT recommends a 4 or 6 dose schedule (D1/D5/D12/D19 or D1/D3/D5/D8/D12/D19), all subsequent cohorts will be treated with a 4 or 6 dose schedule. If on Schedule A **(CLOSED)** or C, all subjects will be pre-treated with an 8 mg dose of IV dexamethasone within 1 hour prior to D1, D3 (if applicable), D5, and D8 (if applicable) AMG 427 doses and each dose step. A dose step is any AMG 427 dose that is higher for a given subject than the subject has previously received. A dose step will be triggered by the observation of CRS or infusion related reaction at the first dose (see example in Figure 2). Dose steps may occur at the D3, D5, D8, D12, or D19. Each cycle will last for approximately 14 days for cohorts receiving 2 or 4 doses (D1/D5 or D1/D3/D5/D8), and approximately 28 days for cohorts receiving 4 or 6 doses (D1/D5/D12/D19 or D1/D3/D5/D8/D12/D19). Subjects will be assessed for DLTs for 28 days. Cycles will be followed by a treatment-free interval for 1-2 weeks (depending on response), which may be extended for up to 7 weeks or longer for the cohorts at higher doses, based on a dose level review meeting (DLRM) recommendation. The D3, D5, D8 doses, and the D12, D19 doses (if applicable) may be at the same dose as the preceding dose or may be at a higher dose level (dose step). This will be based on tolerability of the lower dose level and other clinical signs, pharmacological, and PD results and will be recommended by the DLRT. For a schematic description of the different dose step options see Figure 2 in Section 3.1. For logistical reasons, there is a $\pm$ 1 – 3 day window for dosing days.

Dose Escalation Cohorts

Dose escalation will be conducted in 2 stages: a single subject stage and a multiple subject stage. Single subjects will be enrolled at initial dose levels. Multiple subject cohorts, which will enroll 2 – 4 subjects per cohort, will be triggered by any evidence of pharmacologic activity, including, but not limited to infusion reactions, CRS, tumor lysis syndrome (TLS), or depletion of peripheral blasts and/or white blood cells. The Bayesian logistic regression model (BLRM) design will be used to guide dose escalation. The actual dose selected at each dose cohort may be at or below the model's recommended dose as recommended by the DLRT after considering all information. Subjects will be assessed for DLTs for 28 days. Subjects in the etanercept (Enbrel) substudy **(CLOSED)** can intra-subject dose escalate after 1 cycle to the first-in-human (FIH) study (eg, move from schedule B to schedule C), if subjects show evidence of disease progression after discussion with the Sponsor (eg, use of hydroxyurea to control increasing WBC). Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT, after consultation with the sponsor, if no DLT was reported during or after the completion of the DLT period for that subject.

Estimation of initial and target MTDs

It is anticipated that 2 to 3 MTDs may be estimated: 1 for the initial dosing and 1 - 3 for the subsequent dosing. Should the initial dose be limited by adverse events related to first dose effects and/or cytokine release syndrome, the second MTD (dose step) for the target dose will be estimated after giving the initial dose at MTD1. Each MTD will be estimated following the dose escalation guided by BLRM described above. A second dose step may also be implemented in a cycle if this was considered appropriate and necessary to allow further dose escalation. This second dose step would be performed the same way as described above. In this case, a third MTD would be estimated for the dose to be administered after the second dose step.

Once the dose escalation phase has determined a final MTD, tocilizumab may be evaluated as an alternative prophylaxis to prevent/reduce the severity of CRS. A cohort of 3 subjects may be treated with AMG 427 at the final MTD dose level and a single dose of 8 mg/kg IV tocilizumab will

be administered prior to the dose of AMG 427 replacing pretreatment with dexamethasone. If no DLTs are observed, 3 additional subjects will be included in this cohort. The use of tocilizumab may be further explored based on observed tolerability and other clinical and pharmacological data.

Expansion Cohort

At completion of the dose escalation cohorts, approximately 90 additional subjects (approximately 40 R/R AML subjects in the FIH cohorts and 50 MRD+ AML subjects in the MRD+ cohorts) will be enrolled in a dose expansion cohort to gain further clinical experience, safety, and efficacy data in subjects administered AMG 427. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. Based on emerging safety data, the planned dose level and dose schedule may be modified during the conduct of the expansion phase. Additionally, enrollment to dose expansion will be paused and possibly terminated if safety stopping rules and/or efficacy futility rules are met (see Section 10.3 for details).

A final estimate of the MTD and RP2D will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose escalation and the dose expansion cohorts.

Sample Size:

It is anticipated that approximately 2**0**0 subjects will be enrolled in this study, with approximately 1**1**0 subjects enrolled in the dose escalation cohorts and 90 subjects in the dose expansion cohorts:

Dose escalation cohorts:

- FIH (R/R AML): approximately 90 subjects
  - **(CLOSED)** etanercept substudy (R/R AML): approximately 25 subjects
- eIV (R/R AML): approximately 10 subjects
- MRD Group (MRD+): approximately 10 subjects

Dose expansion cohorts:

- FIH (R/R AML): approximately 40 subjects
- MRD Group (MRD+): approximately 50 subjects

The sample size in the dose escalation is based on practical considerations and is consistent with conventional oncology studies with the objective to estimate the MTD. With 2 subjects per cohort, there is a 19% to 55% probability of observing at least 1 DLT. With 3 subjects per cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 4 subjects per cohort, there is a 34% to 80% probability.

In the dose expansion cohort, a subject number of 40 will provide an 87% probability of observing at least 1 adverse event with 5% incidence rate and 99% probability of observing at least 1 adverse event with 10% incidence rate. A subject number of 50 will provide a 92.3% probability of observing at least 1 adverse event with 5% incidence rate and 99.5% probability of observing at least 1 adverse event with 10% incidence rate. These probabilities will be 64% and 88% respectively with a subject number of 20. An exact 80% binomial CI will be provided for response rate. With the 20 subjects and 20% response rate, the expected 80% CI would be 9% to 36%. With 40 subjects and 20% response rate, the expected 80% CI would be 12% and 30%. With 50 subjects and a 40% response rate, the expected 80% CI would be 30.6% and 50.1%.

Summary of Subject Eligibility Criteria:

Male or female subjects ≥ 18 years of age at the time of signing informed consent who have AML as defined by 2016 World Health Organization (WHO) Classification (Appendix D); for R/R AML subjects only, persisting or recurring following 1 or more treatment courses (choice of treatment courses may be at investigator discretion), and must have ≥ 5% blasts in bone marrow. Patients with acute promyelocytic leukemia (APML) are not eligible for this trial. For MRD+ AML subjects and for a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

AMG 427 will be manufactured and packaged by Amgen Inc., or its agents, and distributed using Amgen or its agents' clinical study drug distribution procedures.

AMG 427 is supplied as a sterile, preservative-free lyophilized powder for administration after reconstitution with sterile Water for Injection (WFI). After reconstitution with [redacted] mL of sterile WFI, the [redacted] mg/mL AMG 427 drug product is formulated with [redacted] mM glutamic acid, [redacted]% (w/v) sucrose, and [redacted]% polysorbate 80, pH [redacted]. The final container is a single-use, 6R glass vial and contains a target extractable amount of [redacted] mg AMG 427.

The intravenous solution stabilizer (IVSS) is supplied as a sterile solution in a [redacted]-cc glass vial containing [redacted] mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted] mM citric acid, [redacted] M lysine hydrochloride, [redacted]% [w/v] polysorbate 80, pH [redacted]). The IVSS is intended for pre-treatment of IV bags prior to dilution of AMG 427 drug product.

AMG 427 solution will be prepared in bags for short or eIV infusion and delivered through infusion lines.

The first eIV group will start at **a** DLRT-approved dose level from the FIH group, eg, if DLRT approves as safe and tolerable, the following dosing regimen will be administered:

- Days 1 and 2: eIV of [redacted] μg (over approximately 48 hours, with approximately 12-hour bag changes)
- Day 3: eIV of [redacted] μg (over approximately 24 hours, with approximately 12-hour bag changes)
- Day 5: short IV of [redacted] μg (over approximately 90 minutes)
- Day 8: short IV of [redacted] μg (over approximately 90 minutes)

Subsequent eIV cohorts will use the same dose levels as the FIH (short IV) cohorts (Table 4).

The infusion-free interval prior to the start of the following treatment cycle will have a duration of 1 to 5 weeks (depending on treatment response and adverse events), but may be extended to up to 7 weeks in case of prolonged marrow aplasia and aleukemic cytopenias after consultation with the sponsor. It may also be extended for up to 3 days from the planned duration if necessary for logistical reasons. The DLRT may recommend on changes of the duration of the infusion-free interval for future cohorts after evaluation of emerging data.

Subjects will be hospitalized for a minimum of 8 or 11 days from the first dose in cycle 1 (ie, at least 72 hours after the day 5 or day 8 dose, depending on the schedule) and for a minimum of 72 hours following day 12 and day 19 doses in cycle 1 (if applicable). If the subject receives a second cycle of AMG 427 at the same dose, hospitalization will be for a minimum of 8 or 11 days from the start of the day 1 dose (ie, at least 72 hours after the day 5 or day 8 dose, depending on the schedule) in cycle 2. Hospitalization following day 12 and day 19 doses (if applicable) in cycle 2 and onwards will be at the discretion of the treating physician. For subjects receiving $>$ 2 cycles, hospitalization for cycle 3 onwards for all doses will be at the treating physician's discretion. However, in case of intra-subject dose escalation (ISDE), subjects will be hospitalized as per the guidance for the first cycle. After re-start of treatment, following an interruption due to an adverse event(s), the subject will be hospitalized for a minimum of 72 hours. Subjects can be hospitalized for a longer time period at the discretion of the investigator. A nurse trained in emergency procedures or a physician must be available when the dose of AMG 427 is started for immediate intervention in case of complications.

The planned dose levels for the dose escalation cohorts are: [redacted] μg. Lower intermediate doses may be implemented based on BLRM and DLRT recommendations. The MTD or a lower dose will be administered in the dose expansion cohort.

A total of up to 12 total treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit and does not meet the criteria for permanent discontinuation of the drug (Section 6.2.1.4).

Procedures:

After providing informed consent, eligible subjects will undergo the following assessments during this study: physical examination, Eastern Cooperative Oncology Group (ECOG) status, height, weight, vital signs, pulse oximetry, electrocardiogram (ECG) triplicate measurements, laboratory assessments (including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, and [redacted]), biomarker and PK assessments, and bone marrow assessments. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 of the study protocol and the Schedule of Assessments (Table 10 to Table 23).

Statistical Considerations:

All subjects who are enrolled and receive at least 1 administration of the investigational product (AMG 427) will be included in the analysis, unless otherwise specified. The primary analysis will occur when target enrollment is complete and each subject either had the opportunity to receive up to 12 cycles of treatment or terminated the study early.

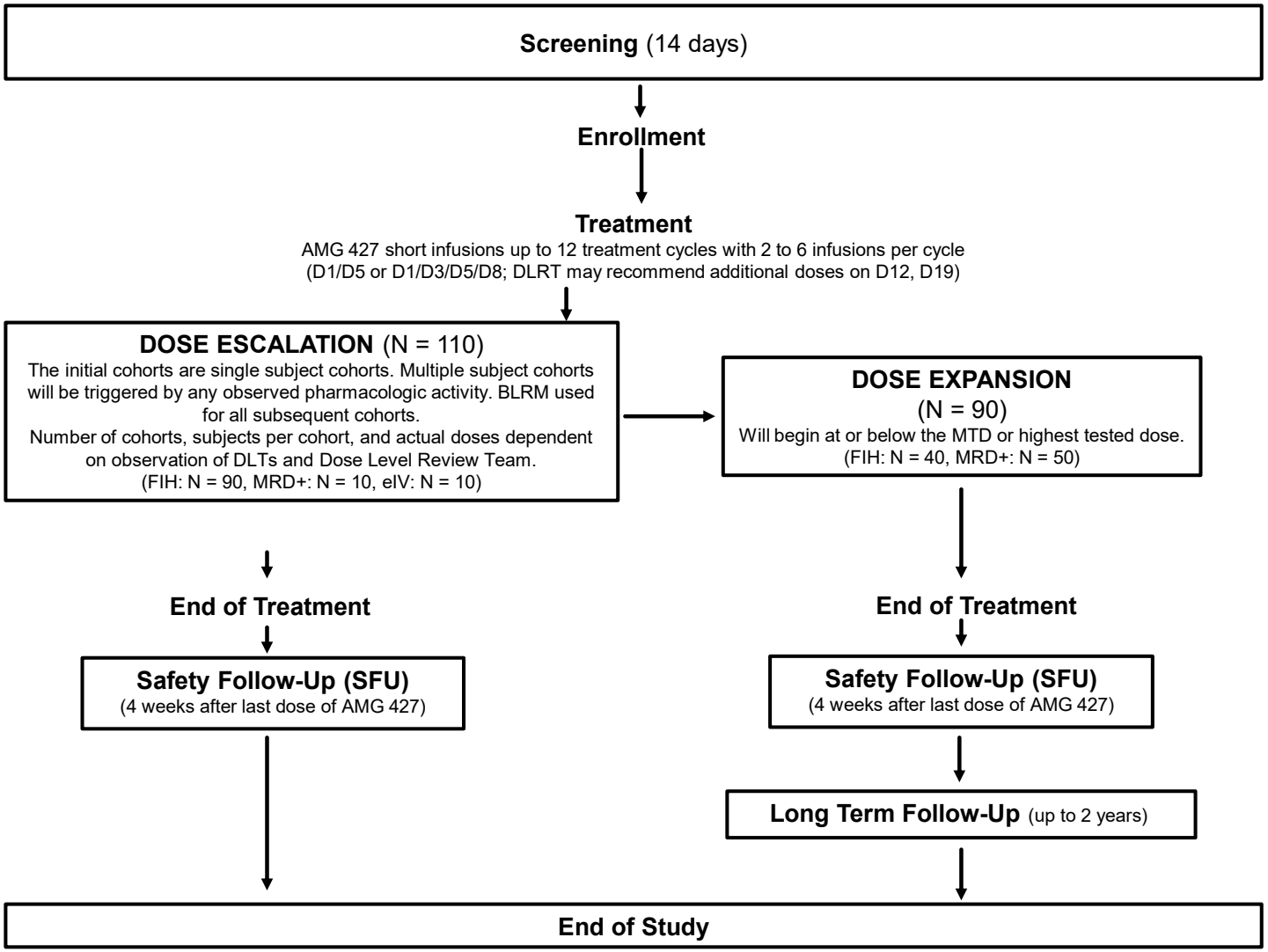
Descriptive statistics will be provided for selected demographics, safety, PK, PD, and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using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

The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated. Clinical laboratory test, ECG, physical examination findings, and vital sign data will be presented. Depending on the size and scope of changes in clinical laboratory, physical examination and vital sign data, the summaries of laboratory, physical examination, and vital sign data over time and/or changes from baseline over time may be provided. Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

The proportion of responding subjects in R/R AML, defined as any of the following: CR, CRi, CRh, morphologic leukemia-free state, and PR with corresponding exact 80% CI, will be calculated using the Clopper-Person method (Clopper and Person, 1934) and tabulated for subjects treated at the estimated MTD. For MRD+ AML, the MRD conversion rate will be presented with corresponding exact 80% CI and tabulated by group and for all subjects treated at the MTD. Efficacy related endpoints (eg, duration of the response) will be presented per subject and Kaplan-Meier estimates may also be further presented if data allows. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
[redacted]	
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APML	acute promyelocytic leukemia
AST	aspartate aminotransferase
ASTCT	**American Society for Transplantation and Cellular Therapy**
AT III	antithrombin III
AUC	area under the concentration-time curve
AUC_{72h}	area under the concentration-time curve from time 0 to 72 hours
AUC_{336h}	area under the concentration-time curve from time 0 to 336 hours
BID	twice a day
BiTE®	bispecific T cell engager
BiPAP	**bilevel positive airway pressure**
BLRM	Bayesian logistic regression model
BM	bone marrow
CAR-T	chimeric antigen receptor T cell
CD3	cluster of differentiation 3
CD19	cluster of differentiation 19
CD33	cluster of differentiation 33
CD135	cluster of differentiation 135
CI	confidence interval
cIV	continuous intravenous
CL	systemic clearance
CL_D	intercompartmental distribution
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CNS	central nervous system
COVID-19	**coronavirus disease 2019**
CPAP	**continuous positive airway pressure**
CR	complete response/remission (see Appendix E for details)
CRF	case report form
CRi	complete response/remission with incomplete recovery of peripheral blood counts (see Appendix E)

Abbreviation or Term	Definition/Explanation
CRh	complete response/remission with partial hematologic recovery (see Appendix E for details)
CRM	continual reassessment method
CRP	C-reactive protein
CRS	cytokine release syndrome
CT (scan)	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentrations
D1	day 1
D5	day 5
D8	day 8
D12	day 12
D19	day 19
DILI	drug-induced liver injury
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	dose-limiting toxicity
EC_{50}	half maximal effective concentration: concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum
EC_{90}	concentration of a drug, antibody or toxicant which induces a response that is 90% of the maximum response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	**electroencephalogram**
eGFR	estimated glomerular filtration rate
eIV	extended intravenous
End of Study (primary completion)	Defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures/assessments are conducted for an individual subject.
ELN	European Leukemia Network
EOI	end of infusion
EOL-1	human acute myeloid (eosinophilic) leukemia cell line

Abbreviation or Term	Definition/Explanation
EOS	end of study - Defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
EOT	end of treatment - defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
EpCAM	epithelial cell adhesion molecule
eSAE	electronic serious adverse event (form)
FAB	French-American-British
Fc	fragment crystallizable
FDA	Food and Drug Administration
FIH	first-in-human
FLT3	fms-like tyrosine kinase 3
FLT3L	FLT3 ligand
GCP	Good Clinical Practice
GLP	Good Laboratory Practice(s)
Heart rate	number of cardiac cycles per unit of time
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C virus antibody
HiDAC	high-dose cytarabine
HIV	human immunodeficiency virus
HLE	half-life extended
HLH	**hemophagocytic lymphohistiocytosis**
HNSTD	highest non-severely toxic dose
HSCT	hematopoietic stem cell transplant (or transplantation)
IB	investigator's brochure
ICANS	**immune effector cell-associated neurotoxicity syndrome**
ICE	**immune effector cell-associated encephalopathy**
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICP	**intracranial pressure**
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
IEC	independent ethics committee
IFN γ	interferon gamma
IgG	immunoglobulin G

Abbreviation or Term	Definition/Explanation
IL-1Ra	**interleukin-1 receptor antagonist**
IL-2	interleukin-2
IL-6	interleukin-6
INR	international normalized ratio
IRB	institutional review board
ISDE	intra-subject dose escalation
ITD	internal tandem duplication
IUD	intrauterine device
IV	intravenous
IVSS	intravenous solution stabilizer
IWG	International Working Group
KDM	kinase domain mutation(s)
LAIP	leukemia-associated immunophenotype
LDH	lactate dehydrogenase
[redacted]	
LTFU	long-term follow-up
MABEL	minimum anticipated biological effect level
MDS	myelodysplastic syndrome
MLFS	**Morphologic Leukemia Free State**
MOLM-13-luc	human acute myeloid leukemia cell line genetically-engineered to express luciferase
Morphologic leukemia-free state	less than 5% blasts in bone marrow without recovery of peripheral blood counts (see Appendix E for details)
MPN	myeloproliferative neoplasm
MRD	minimal/measurable residual disease
MRD-	minimal/measurable residual disease-negative
MRD+	minimal/measurable residual disease-positive
MRI	contrast-enhanced magnetic resonance imaging
MTD	maximum tolerated dose
NGS	next generation sequencing
NOD/SCID	non-obese diabetic/severe combined immunodeficiency disease
NPM1	Nucleophosmin 1
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic(s)

Abbreviation or Term	Definition/Explanation
PK	pharmacokinetic(s)
PG	Pharmacogenetic(s)
PPD	purified protein derivative
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
RP2D	recommended phase 2 dose
R/R	Relapsed/refractory
RR interval	The time elapsed between 2 consecutive R waves as measured by ECG
RT-PCR	**reverse transcriptase-polymerase chain reaction**
SARS-CoV-2	**severe acute respiratory syndrome coronavirus 2**
sc	single chain
sFLT3	soluble FLT3
SCR	Screening
SFU	safety follow-up
SOC	System Organ Class
Source Data	Information from an original record or certified copy of the original record containing information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
study day 1	defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
SVR24	sustained virologic response 24 weeks after completion of anti-hepatitis C treatment
$t_{1/2}$	terminal-phase elimination half-life
TBIL	total bilirubin
TEAE	treatment-emergent adverse event(s)
TID	3 times a day
TK	toxicokinetic(s)

Abbreviation or Term	Definition/Explanation
TKD	tyrosine kinase domain
TLS	tumor lysis syndrome
T_{max}	time of maximum concentration
TNF	tumor necrosis factor
TPI	toxicity probability interval
TREA	treatment-related adverse events(s)
ULN	upper limit of normal
US	United States
V_c	volume of distribution of central compartment
V_p	peripheral volume of distribution
WBC	white blood cell(s)
WFI	Water for Injection
WHO	World Health Organization

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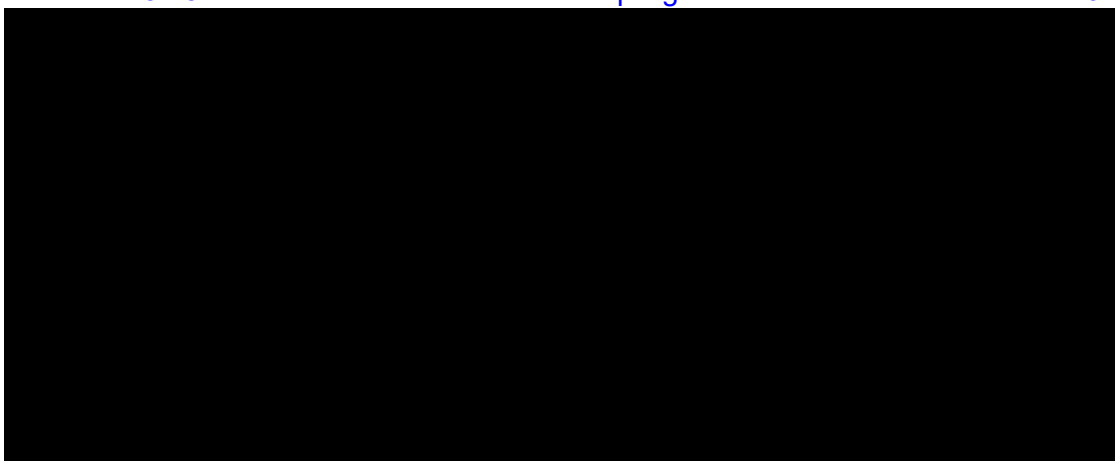

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1. OBJECTIVES

1.1 Primary

The primary objectives of this study are to:

- Evaluate the safety and tolerability of AMG 427 in adult subjects with relapsed/refractory (R/R) acute myeloid leukemia (AML) or minimal/measurable residual disease-positive (MRD+) AML
- Estimate the maximum tolerated dose (MTD) and/or a biologically optimal dose (eg, recommended phase 2 dose [RP2D])
- Evaluate the safety and tolerability of extended intravenous (eIV) **administration of** AMG 427.

1.2 Secondary

The secondary objectives of this study are to:

- Characterize the pharmacokinetics (PK) of AMG 427
- Evaluate the anti-leukemia activity of AMG 427

1.3 Exploratory

2. BACKGROUND AND RATIONALE

2.1 Disease

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults in the United States (US), with a rising incidence possibly due to an aging population, increased environmental exposure (eg, ionizing radiation), and an increase in the population of cancer survivors previously exposed to chemotherapy and therapeutic radiation. In 20**20**, an estimated 19 9**4**0 new cases of AML were expected in the US with approximately 1**1 180** deaths from this disease (American Cancer Society, 20**20**).

The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years (Dohner et al, 2010) although 8 new drugs were approved by the US Food and Drug Administration (FDA) in 2017 and 2018 for various subsets of AML patients (Mylotarg USPI, Rydapt USPI, Idhifa USPI, Vyxeos USPI, Tibsovo USPI, Xospata UPSI, Daurismo USPI, Venclexta USPI). These therapies have added to the therapeutic options for patients with AML, especially those bearing mutations that can be targeted with these novel agents (eg, FLT3 tyrosine kinase domain [TKD], isocitrate dehydrogenase 2 [IDH2] mutation); however, only a small subset of AML patients bear these mutations. AML is cured only in 35% to 40% of adult patients who are 60 years of age or younger and in 5% to 15% of patients who are older than 60 years of age (Dohner et al, 2010). Although the majority of patients with AML initially achieve complete remission (CR), over 60% will eventually relapse after a variable period of remission. The relapse of AML, particularly early after a hematopoietic stem cell transplant (HSCT), is challenging to manage (de Lima et al, 2014). Only 20% to 30% of patients can achieve durable remissions after reinduction in the relapsed setting and the rate of survival after relapse is poor (Dohner et al, 2015). In addition, approximately one-third of patients younger than 60 years with newly diagnosed AML fail to achieve CR after induction therapy (Buchner et al, 2012). For these resistant patients, chemotherapy alone does not offer any chance of cure (Estey, 2000). For example, patients with AML refractory to 1 course of a high dose cytarabine (HiDAC) containing regimen have a median overall survival of only 3.8 months (Ravandi, 2013). Patients whose initial CR duration is more than 1 year have been traditionally treated with HiDAC-containing salvage regimens but only a minority achieve a second CR and many are not candidates for a potentially curative allogeneic HSCT performed in second CR (Estey, 2000). Apart from the duration of first CR, other predictors of outcome in first relapse include age, cytogenetics, and whether the patient received an allogeneic HSCT in the first CR (Breems et al, 2005). However, in the study reported by Breems et al (2005), only a minority of patients with AML in first relapse had a successful long term outcome and the long term prognosis of the majority of patients with relapsed or refractory AML remains dismal.

For patients with AML who achieve **CR**, relapsed disease remains the primary obstacle to long-term survival. Consolidation therapy and allogeneic HSCT decrease the risk of relapse for many patients, but rates of relapse still remain high, and overall survival ranges from 2-15% for those with intermediate and adverse-risk genetics (Döhner et al,

2017). Furthermore, due to patient performance status and comorbidities, many AML patients are not eligible for allogeneic HSCT, leaving a subset of patients with no further treatment options (Döhner et al, 2017).

Minimal/measurable residual disease-positive is a proven risk factor for relapse and poor survival in patients with ALL (Richard-Carpentier et al, 2019), and this concept is quickly gaining wider acceptance in the AML community (Buccisano et al, 2018). As minimal/measurable residual disease (MRD) methods and procedures become more harmonized, this post-treatment "biomarker" may lead to significantly more accurate prognostic assessment in AML (FDA Guidance, 2020), with greater predictive and prognostic power than currently available molecular genetic markers (Buccisano et al, 2018). As such, the National Comprehensive Cancer Network Guidelines recommend MRD testing after induction therapy (www.nccn.org/professionals/physician_gls/pdf/aml_blocks.pdf), and the European LeukemiaNet endorses the achievement of MRD-**CR**, noting the strong correlation between MRD negativity and increased survival (Schuurhuis et al, 2018).

Unlike for ALL patients, where blinatumomab is effective at converting MRD+ status and prolonging survival (Jen et al, 2019), no approved MRD treatment options exist for AML patients. When combined with the large proportion of AML patients who are HSCT-ineligible, a significant unmet medical need exists for this group. For AML patients, several clinical trials are currently underway in order to determine additional frontline, MRD+, and maintenance therapies, that will reduce relapse rates. These include chimeric antigen receptor T-cell (CAR-T) and other cell-based therapies (NCT03190278), mutation-specific targeted small molecules (NCT03070093, NCT02927262, NCT03850535, NCT03515512, NCT03728335), other small molecules (NCT00387647, NCT02126553, NCT00350818), chemotherapy (NCT02349178), and an anti-CD33 antibody-drug conjugate (NCT03705858).

2.2 Amgen Investigational Product Background

AMG 427, which targets FLT3 and engages host T cells via cluster of differentiation 3 (CD3) binding, is an FDA-designated FastTrack novel bispecific T cell engager (BiTE®) molecule intended to treat patients with AML. AMG 427 is a half-life extended (HLE) BiTE® **molecule** combining the binding arms for FLT3 and CD3 genetically fused to the N-terminus of a single chain (sc) immunoglobulin G (IgG) Fc (fragment crystallizable; scFc) region. The anticipated terminal half-life of AMG 427 in humans is expected to be approximately 5 days. This key HLE modification, designed to

maintain efficient FLT3 dependent target cell killing, should permit intermittent short IV infusions to be delivered over a course of several days up to 2 to 3 weeks.

In addition to AMG 427, Amgen is developing other novel BiTE® molecules that target different antigens for the treatment of patients with AML.

Refer to the specific section of the AMG 427 investigator's brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.2.1 Nonclinical Pharmacology

In vitro Pharmacology:

The activity of AMG 427 requires the simultaneous binding to $FLT3^+$ cells and T cells. The pharmacological effect of AMG 427 is mediated by specific redirection of cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to kill FLT3-expressing cells. AMG 427 is a potent molecule showing half maximal-lysis (EC_{50}) of FLT3-expressing tumor cell lines by human T cells in vitro over a range from 2.24 to 12.03 pM.

As part of the T cell activation process, BiTE® **molecules**, such as AMG 427, cause the formation of a cytolytic synapse between T cells and target cells, which has been exemplified for an EpCAM-specific BiTE® **molecule**. The subsequent release of the pore-forming protein perforin and the apoptosis-inducing proteolytic enzyme granzyme B by T cells results in the induction of apoptosis in the target cells (Offner et al, 2006).

In serum of AML patients, elevated levels of soluble FLT3 (sFLT3) were observed (Ravandi et al, 2007). Although maximal AMG 427-mediated redirected lysis was not affected in vitro, EC_{50} values of dose-response curves of cytotoxicity and T cell activation were higher in the presence of physiologically relevant sFLT3 concentrations. In the absence of membrane bound FLT3, sole binding of sFLT3 to AMG 427 was not sufficient to induce T cell activation.

In addition, FLT3 ligand (FLT3L) has been detected in serum of AML patients (Sato et al, 2011; Zwierzina et al, 1999). In in vitro cytotoxicity assays, maximal target cell lysis was not affected by recombinant FLT3L, however, EC_{50} values calculated for AMG 427 dose-response curves of target cell lysis and T cell activation increased in the presence of recombinant FLT3L.

The efficacy of AMG 427 was also evaluated in bone marrow aspirates obtained from an AML patient comprising $FLT3^+$ leukemic cells, but no autologous T cells.

AMG 427 induced a dose-dependent decrease of viable leukemic cells in co-cultures with allogeneic T cells isolated from a healthy donor.

AMG 427-induced T cell activation not only caused redirected lysis of $FLT3^+$ cells, but also resulted in a transient production of inflammatory cytokines like tumor necrosis factor (TNF), interferon gamma (IFN γ), interleukin-2 (IL-2), and interleukin-6 (IL-6) by T cells. In addition, in vitro studies also demonstrated that cytokine release by AMG 427-activated T cells is attenuated by corticosteroids, which is accompanied by a slight reduction in cytotoxic potency.

In vivo Pharmacology:

Orthotopic mouse xenograft models using human MOLM-13-luc and EOL-1 AML tumor cell lines were used for the evaluation of the nonclinical in vivo efficacy of AMG 427 (Studies 124021 and 125009). The AML cell lines were intravenously (IV) injected into the lateral tail vein of nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice. Since AMG 427 does not recognize mouse CD3, the NOD/SCID mice were intraperitoneally injected with human T cells before treatment start. AMG 427 monotherapy significantly prolonged of mice bearing established orthotopic MOLM 13-luc or EOL 1 tumors.

2.2.2 Nonclinical Pharmacokinetics

The PK and toxicokinetics (TK) of AMG 427 were characterized in cynomolgus monkeys. After intravenous (IV) bolus injection, serum concentrations of AMG 427 declined in a bi-phasic manner. The maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC) were approximately dose proportional from [redacted] μg/kg.

The human PK parameters of AMG 427 were predicted using allometric scaling of PK parameters obtained from cynomolgus monkeys. A 2-compartment model with linear elimination was used to characterize the AMG 427 PK from the pooled data with doses ranging between [redacted] μg/kg. The model was parameterized using linear clearance (CL), volume of distribution of central compartment (V_C), intercompartmental distribution rate (CL_D), and peripheral volume of distribution (V_P).

2.2.3 Nonclinical Toxicology

The nonclinical safety assessment of AMG 427 was based on a 28-day cynomolgus monkey repeat dose IV injection study. The cynomolgus monkey was selected as the toxicology species based on target binding affinity and bioactivity data similar to human.

Flat doses of [redacted] μg/kg were administered on days 1, 5, and once weekly thereafter. Vehicle control or a step dose of [redacted] μg/kg was administered on days 1 ([redacted] μg/kg), 5 ([redacted] μg/kg), 8 ([redacted] μg/kg), 12 ([redacted] μg/kg), and once weekly thereafter ([redacted] μg/kg). The flat dose regimen of [redacted] μg/kg and the step dose regimen of [redacted] μg/kg showed no adverse effects. Results in these animals and in animals administered the flat dose of [redacted] μg/kg that survived to the end of the study were consistent with expected AMG 427 pharmacology (cytotoxic T cell redirected lysis of FLT3-expressing bone marrow hematopoietic stem and progenitor cells). AMG 427-related changes on days 1 and/or 2 were consistent with AMG 427-mediated T cell activation and included elevated heart rate, transient increases in cytokine levels, decreased circulating leukocytes, and clinical chemistry changes suggestive of an acute phase response. At the end of the study, decreased bone marrow cellularity, decreased white blood cells, decreased neutrophils, decreased red blood cell mass associated with attenuated or decreased reticulocytes, and decreased platelets were observed. Increased bone marrow cellularity and lymphoid germinal center cellularity in lymph nodes and/or spleen were attributed to a regenerative response following initial activity of [redacted] Administration of the flat dose regimen of [redacted] μg/kg resulted in mortality in 5 out of 10 animals on days 18 to 26. [redacted]. Decreased bone marrow cellularity was consistent with expected AMG 427 pharmacology (cytotoxic T cell redirected lysis of FLT3 expressing bone marrow hematopoietic stem and progenitor cells) and bacteremia was secondary to the decrease in myeloid cells and subsequent decreased innate immunity. [redacted]

Thus, the highest non-severely toxic dose (HNSTD) for the flat dose regimen is [redacted] μg/kg and the HNSTD for the step-dose regimen ([redacted]) is [redacted] μg/kg.

2.2.4 Clinical Experience With AMG 427

As of the 26 July 2021 data cutoff, a total of 54 subjects with R/R AML were enrolled in the first-in-human (FIH) Amgen Study 20170528. Of the 54 subjects,

there were 53 subjects who received at least 1 dose of AMG 427 or etanercept (51 subjects received AMG 427 and 10 subjects received etanercept including 2 subjects who received etanercept only). One subject enrolled in cohort [redacted] was treated with AMG 427 but did not have exposure data entered into the database by the data cutoff date and was therefore not included in the Safety Analysis Set.

Summary of Safety Findings: Fifty-three subjects (100%) who received at least 1 dose of AMG 427 or etanercept had treatment-emergent adverse events. Adverse events by preferred term reported for ≥ 20.0% of subjects were cytokine release syndrome (42 subjects [79.2%]); hypokalemia and pyrexia (13 subjects each [24.5%]), febrile neutropenia (12 subjects [22.6%]), and hypomagnesemia (11 subjects [20.8%]). Grade ≥ 3 treatment-emergent adverse events were reported for 46 subjects (86.8%). The grade ≥ 3 adverse events reported in ≥ 2 subjects included anemia (4 subjects [11.8%]); febrile neutropenia (7 subjects [20.6%]); white blood cell count decreased (4 subjects [11.8%]); bacteremia, sepsis, sinusitis, hypophosphatemia (3 subjects [8.8%] each); and leukocytosis, pancytopenia, cytokine release syndrome, pneumonia, alanine aminotransferase increased, lipase increased, white blood cell count increased, hypokalemia, acute myeloid leukemia, epistaxis, respiratory distress, and respiratory failure (2 subjects [5.9%]). Treatment-emergent serious adverse events were reported for 34 subjects (64.2%). Preferred terms for these serious adverse events reported for > 1 subjects were cytokine release syndrome (8 subjects [15.1%]), acute myeloid leukemia and febrile neutropenia (5 subjects [9.4%] each), pneumonia (3 subjects [5.7%]), and sepsis, septic shock, sinusitis, leukocytosis, respiratory distress, decreased platelet count, and decreased white blood cell count (2 subjects [3.8%] each). Eleven subjects (20%) had treatment-emergent fatal adverse events of acute myeloid leukemia (2 subjects each), anemia, bacillus infection, cytokine release syndrome, fungal sinusitis hemophagocytic lymphohistiocytosis (HLH), intracranial hemorrhage, pneumonia, respiratory distress, and respiratory failure (1 subject each).

Overall, 42 (79.2%) of the 53 subjects exposed to AMG 427 or etanercept reported 1 or more adverse events of CRS. No subjects enrolled in cohorts [redacted] reported any adverse events of CRS, while at least 1 subject in each of the remaining cohorts (target and step dosing) reported 1 or more adverse events of

CRS. Most subjects reported low grade (grade 1 or grade 2) CRS. Subject incidence of grade 1 or grade 2 CRS was 6 (11.3%) and 31 (58.5%), respectively. Four (7.5%) subjects reported grade 3 CRS (1 subject in cohort [redacted] after receiving a day 1 dose of [redacted] µg, 1 subject in cohort [redacted] after receiving a day 1 dose of [redacted] µg, 1 subject in cohort [redacted] after receiving a day 5 dose of [redacted] µg, and 1 subject in the etanercept substudy cohort [redacted]) and a single (1.9%) subject had a grade 5 (fatal) CRS event (1 subject in cohort [redacted] after receiving a day 5 dose of [redacted] µg). Eight (15.1%) events of CRS were considered serious adverse events. Subject incidence of adverse events of CRS leading to hospitalization in the intensive care unit (ICU), interruption of AMG 427, or discontinuation of AMG 427 were 4 (7.5%), 4 (7.5%), and 2 (3.8%) subjects, respectively. Please refer to the AMG 427 Investigator's Brochure for additional details.

A fatal case of 'possible HLH' was reported in the AMG 427 etanercept substudy. The fatal event was reported in a [redacted]-year-old male with refractory AML. No confirmatory bone marrow biopsy for HLH, or autopsy was performed. The subject had multiple confounding factors for the diagnosis of HLH. The subject's ferritin was elevated (4902 µg/dL) 5 days prior to starting AMG 427, and 3 days prior to starting etanercept. Hemophagocytic lymphohistiocytosis can also be caused by infection; the subject had worsening neutropenia, although no additional cultures were reported. Hemophagocytic lymphohistiocytosis is known to occur in approximately 9% of patients with AML after intensive induction therapy (Delavigne et al, 2014). There is a possible contributory role for etanercept and tocilizumab in this case. Macrophage activation syndrome is listed as an adverse reaction for Enbrel (Enbrel® USPI, 2017 [Section 6.3 Postmarketing Experience]) and events of macrophage activation syndrome occurred in patients treated with tocilizumab (Actemra® USPI, 2021 [Section 6.7 Clinical Trials Experience]).

Refer to the Investigator's Brochure for additional detail on these safety findings.

<u>Summary of efficacy findings</u>: Best overall response observed to date included 1 subject in cohort [redacted] µg) achieving CR, a second subject in cohort [redacted] µg) achieving CR with incomplete recovery of peripheral blood counts (CRi) with MRD negativity by flow cytometry, and 4 subjects achieving Morphologic Leukemia Free State (MLFS): 1 subject each in cohort [redacted] µg), cohort [redacted] µg), cohort [redacted] µg) and

cohort [redacted] µg). Please refer to the Investigator's Brochure for additional details.

2.2.5 Clinical Experience With Other BiTE® Molecules

BiTE® **molecules** exert a unique but also uniform mechanism of action independent from their respective target. Consequently, experiences with other BiTE® **molecules** are regarded as being relevant for AMG 427.

Most clinical experience exists with a BiTE® molecule called blinatumomab (specificity for CD3 and cluster of differentiation 19 [CD19]) which has shown that administration of a BiTE® by continuous IV (cIV) infusion can be performed with an acceptable safety profile and leads to improvement in overall survival in subjects with late-stage hematological malignancies (Kantarjian et al, 2017). Blinatumomab is approved in the US under the tradename Blincyto® for the treatment of relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL) and MRD-positive B-ALL (Blincyto USPI). The most common adverse reactions (≥ 20%) are infections, pyrexia, headache, infusion- related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. In addition, Amgen is testing 2 BiTE® molecules targeting cluster of differentiation 33 (CD33) in active clinical development in patients with AML.

2.3 Risk Assessment

FLT3 is a transmembrane tyrosine kinase that stimulates survival and proliferation of blasts (Daver and Kantarjian, 2017). AMG 427 targets FLT3 on AML cells and CD3 on host T cells.

Based on the mode of action targeting membranous FLT3 and clinical observations with **AMG 427 and** other BiTE® molecules developed in hematological malignancies, adverse events such as CRS, cytopenia, hemorrhage, tumor lysis syndrome (TLS), and infection are anticipated with the administration of AMG 427. Neurotoxicity has been observed with the administration of blinatumomab (CD19 BiTE®). For a listing of important potential and identified risks for AMG 427 refer to Table 1 and Table 2 below. See also Section 6.6 for specific recommendations for CRS grading and management, TLS, and infection prophylaxis.

Please refer to the AMG 427 Investigator's Brochure for further description of potential risks.

Table 1. Important Identified Risks of AMG 427

Risk	Description
Cytokine Release Syndrome (CRS)/Infusion Reactions	**Cytokine release is an anticipated consequence of T cell engagement induced by AMG 427. Serious events of cytokine release syndrome, including a fatal event, have been reported in subjects receiving AMG 427. Cytokine release syndrome is characterized by a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity, neurologic function, and heart, lung, liver, and kidney functions.** Signs and Symptoms may include the following: • constitutional - fever, rigors, fatigue, malaise • neurologic - headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • respiratory - dyspnea, tachypnea, hypoxemia • cardiovascular - tachycardia, hypotension • gastrointestinal - nausea, vomiting, transaminitis, hyperbilirubinemia • hematology - bleeding, hypofibrinogenemia, elevated D-dimer • skin – rash **Potentially life-threatening complications of cytokine release syndrome include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (Lee et al, 2014).** Infusion reactions may be clinically indistinguishable from manifestations of CRS

Table 2. Important Potential Risks of AMG 427

Risk	Description
Cytopenia	Transient myelosuppression including reductions in circulating neutrophils, platelets, and red cell mass
Hemorrhage	Bleeding complications, such as disseminated intravascular coagulation syndrome, are due to the massive intravascular activation of blood coagulation with consumption of clotting factors and platelets, leading to severe hemorrhages.
Tumor lysis syndrome	Complications caused by the breakdown products of dying cancer cells may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure.
Infections	Immunocompromised patients are susceptible to both common community-acquired and opportunistic infections. Subjects who have neutropenia for 7 days or more are at a high risk for infectious complications.
Neurotoxicity	A wide range of commonly observed neurological symptoms **otherwise recognized as immune effector cell-associated neurotoxicity syndrome (ICANS)** have been associated with the use of blinatumomab (anti-CD19 BiTE® **molecule**) in patients with R/R ALL and included tremor, dizziness, encephalopathy, paresthesia, aphasia, and confusional

Risk	Description
	state. The majority of these events occurred during the first cycle. In patients with AML, leptomeningeal involvement is expected to be much less frequently observed (< 3%) than in patients with ALL.

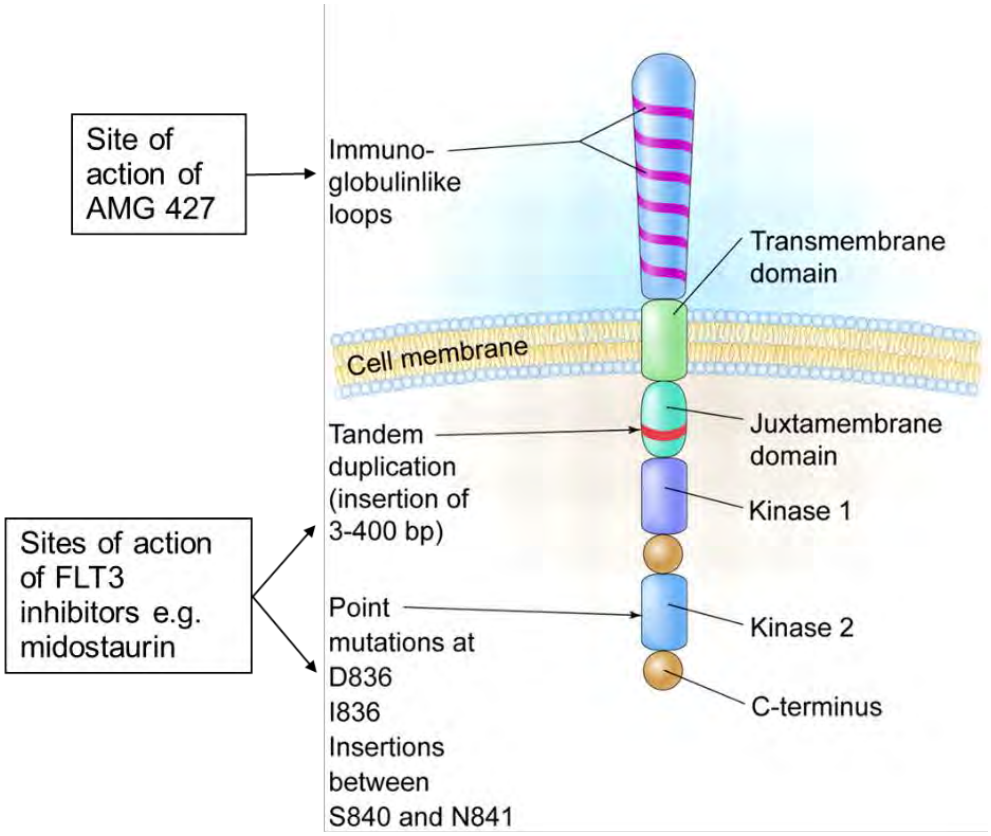
See also Section 2.2.3 for nonclinical safety observations.

2.4 Rationale

2.4.1 Target Rationale

FMS-like tyrosine kinase 3 (FLT3)/cluster of differentiation 135 (CD135) is a member of the class III receptor tyrosine kinases and a type 1 transmembrane protein that plays an essential role in normal hematopoiesis. An internal tandem duplication (ITD) of base pairs within the juxtamembrane coding portion or point mutations in the second kinase domain (KDM) result in constitutive activation of the gene in AML patients. However, only about 1/3rd of AML patients harbor these mutations, which can be targeted by recently approved FLT3 inhibitor midostaurin (Figure 1). In contrast, the immunoglobulin like loop expressed on the cell surface is expressed on more than 80% of leukemia isolates from patients with AML (Goldstein et al, 2017, Meshinchi et al, 2009, Rosnet et al, 1996), providing a useful target antigen for the treatment of patients with AML. FLT3 transcripts are universally detectable in AML blasts with graded expression in distinct FAB (French-American-British) subtypes (Ozeki et al, 2004, Kuchenbauer et al, 2005). Higher FLT3 transcript levels correlate with higher leukocyte counts and higher degrees of bone marrow infiltration by leukemic cells, independent from the presence of FLT3 mutations (Kindler et al, 2010). FLT3 is also expressed on myeloid, lymphoid and dendritic cell progenitors and is considered an important growth and differentiation factor for several hematopoietic lineages (Tsapogas et al, 2017). It is expressed by a fraction of the normal pluripotent hematopoietic stem cells (Rosnet et al, 1996). Targeting membranous FLT3 via CAR-T cell therapy is currently being explored by several groups (Chen et al, 2017, Jetani et al, 2018).

Figure 1. A Schematic Diagram of the FLT3 Receptor Tyrosine Kinase Showing the Location of the Membranous Immune-globulin-like Loops, Internal Tandem Duplication (ITD) of Genes Within the Juxtamembrane Domain and Point Mutations and Gene Insertion in the Second Kinase Domain



Adapted from Litzow M, Blood 2005;106:3331-3332

2.4.2 Target Population Rationale

Target population rationale is described in the background (Section 2.1) and target rationale (Section 2.4.1) sections.

2.4.3 Dose Selection Rationale

The planned doses of AMG 427 in this study are [redacted] µg. AMG 427 will be administered as single, short IV infusions (eIV infusion may apply) on D1/D5 or D1/D3/D5/D8 of a 14-day treatment cycle, in which the second dose on day 3 or 5 may be the same or higher than the dose on day 1. Based on observed safety and tolerability, the day 1 dose may be established as a run-in dose (ie, MTD1), while day 3, 5, or 8 doses may be subsequently escalated. Based on clinical experience from a CD33-targeting BiTE® for R/R AML, the day 1 dose is unlikely to have anti-leukemic effect and will be used primarily to mitigate the risk of cytokine release syndrome following initiation of treatment

or exposure to higher concentrations of AMG 427 that are more likely to have anti-leukemic activity.

The proposed starting dose of AMG 427 in the FIH study is [redacted] µg. This was based on the predicted human dose necessary to provide a maximum serum concentration approximating 0.104 ng/mL, the mean in vitro EC_{50} of AMG 427-mediated CD69-upregulation, and is anticipated to have limited pharmacological activity. AMG 427 human PK profiles and exposures were predicted using a 2-compartment model with linear elimination from the central compartment. Human PK parameters were scaled using allometry from estimated PK parameters in cynomolgus monkey studies described in Section 2.2.2. Based on predicted AMG 427 PK, a starting dose of [redacted] µg following a short IV infusion (approximately 30 minutes to 1 hour) is predicted to achieve maximum serum concentrations approximating the mean EC_{50} of AMG 427 mediated CD69-upregulation in MOLM-13 cells (MABEL; 0.104 ng/mL). Of note, soluble FLT3 concentrations in the ranges observed in serum of AML patients (up to 140 ng/mL) did not have a significant effect on the predicted maximum serum concentrations of AMG 427 (within 2-fold) and were not used in the selection of the FIH starting dose. The use of the EC_{50} as the MABEL and basis for the FIH starting dose is supported by the previous and safe implementation of this strategy to identify the maximum recommended starting doses of previous bi-specific CD3-targeting molecules in clinical development (Saber et al, 2017).

Additionally, mean AUC from time zero to 72 hours (AUC_{72h}) and C_{max} exposures achieved at the HNSTD of the flat dose regimen of [redacted] µg/kg in the 28-day toxicology study in cynomolgus monkeys were approximately 47-fold and 119-fold greater than human AUC from time 0 to 336 hours (AUC_{336h}) and C_{max} exposures predicted at the [redacted] µg starting dose, respectively, after correction for a 10-fold lower potency in cynomolgus monkey effector cells. Of note, relative to the step-dose regimen of [redacted] µg/kg on day 1 followed by a step up to [redacted] µg/kg on day 5, and another step up to [redacted] µg/kg on day 8 and onwards ([redacted] µg/kg) also evaluated in the 28-day toxicology study, AUC_{72h} and C_{max} exposures were approximately 6950-fold and 6180-fold greater than human exposure predictions, after a 10-fold potency correction (Table 3).

Subsequent planned escalations in AMG 427 dose up to [redacted] µg are shown in Table 3. At the highest planned clinical dose of [redacted] µg, the ratio of mean AUC_{72h} and C_{max} exposures achieved at the [redacted] µg/kg HNSTD in the 28-day toxicology study in cynomolgus

monkeys and predicted human AUC_{336h} and C_{max} exposures were approximately [redacted], respectively, after a 10-fold potency difference in human and cynomolgus monkey effector cells (ratio of mean AUC_{72h} and C_{max} exposures achieved at the [redacted] μg/kg HNSTD in the 28-day toxicology study were approximately [redacted] and [redacted] respectively, after potency correction).

[redacted]

Minimally efficacious exposures of AMG 427 were estimated based on the in vitro assessments of AMG 427 activity. Based on the assessment of individual dose-response curves of AMG 427-mediated cell cytotoxicity in 7 different FLT3-expressing AML cell lines, a median EC_{90} of 12.1 pM (1.3 ng/mL) was calculated.

An AMG 427 dose of [redacted] µg is predicted to provide trough coverage of the EC_{90} following day 1 and day 5 administration and is expected to achieve anti-leukemic effect. As FLT3 expression is heterogenous between different AML patients, AMG 427-mediated cytotoxicity in the least sensitive cell line (KG-1 cells) was also used to establish a conservative prediction of efficacy. Based on a mean EC_{90} of cell cytotoxicity in KG-1 cells (35.83 pM; 3.8 ng/mL), an AMG 427 dose of [redacted] µg is predicted to be efficacious. Collectively, minimally efficacious exposures of AMG 427 are predicted at doses of [redacted] µg, following once weekly administration.

As of **26 July** 202**1**, **53** subjects have been treated**, 51** at **AMG 427** doses ranging from [redacted] µg in the ongoing FIH study**, and 2 subjects only receiving etanercept (Enbrel)**. Clinical data show an acceptable safety profile up to doses of [redacted] µg and preliminary PK analysis suggests dose-related increases in AMG 427 C_{max} and AUC across the dose range evaluated. The emerging clinical data from the ongoing FIH study support the exploration of additional dose levels **and regimens** to determine the MTD for AMG 427. Additional doses **and regimens** of [redacted] µg will be explored in the dose escalation part of the study.

The eIV infusion group will enroll the first subjects, as eIV infusion is predicted to be the safest and most conservative dosing regimen (please see Section 3.1.1.2.1-Justification for eIV Investigational Product Dose). Two to 4 subjects will be initially enrolled for the [redacted] cohort. Overall, the dosing regimen will be as follows:

- **Day 1 and 2: eIV infusion of [redacted] µg (over approximately 48 hours)**
- **Day 3: eIV infusion of [redacted] µg (over approximately 24 hours)**
- **Day 5: short IV infusion of [redacted] µg (over approximately 90 minutes)**
- **Day 8: short IV infusion of [redacted] µg (over approximately 90 minutes)**

After Dose Level Review Team (DLRT) determines that the [redacted] µg target dose level and dosing route achieves an acceptable safety profile, then DLRT can recommend dose escalation and opening of additional experimental groups as described below.

2.5 Clinical Hypotheses

AMG 427 will demonstrate evidence of anti-leukemic activity at a safe and well-tolerated dose in subjects with MRD+ or R/R AML.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a FIH, open-label, phase 1 dose escalation study. AMG 427 will be evaluated as a short-term IV infusion **(eIV infusion may apply)** in adult subjects with MRD+ or R/R AML. The study will be conducted at approximately 15 sites in the US, Australia, Canada, Japan, South Korea, and Germany. Additional countries or sites may be added later.

The study will consist of up to a 14-day screening period, a treatment period, a safety follow-up period (SFU), and a long-term follow-up (LTFU) period (for subjects enrolled in the dose expansion phase only).

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 427 in subjects with MRD+ or R/R AML using a Bayesian logistic regression model (BLRM: Neuenschwander et al, 2008). Planned dose levels (dose per infusion) for the dose-escalation cohorts are as follows: [redacted] µg (Table 4). Additionally, an option for cohort escalation will be available for confirming the safety in Japanese population, at sponsor discretion, for up to a maximum of 6 subjects. The sponsor will notify Japanese sites, if applicable, when the extended slots for a cohort are open for enrollment (after the Dose Level Review Team [DLRT] has confirmed the dose level is safe). The study will consist of **3** groups:

- **FIH Group:** AMG 427 **administered as** short term IV infusions in R/R AML subjects.
  - **(CLOSED)** Etanercept (Enbrel®) substudy: Etanercept will be administered for CRS prophylaxis 2 days prior to each cycle of AMG 427 short term IV infusions in R/R AML subjects in the US. (Etanercept may be implemented to FIH expansion groups based on emerging data).
- **eIV Infusion Group:** AMG 427 eIV infusions administered on days 1 **and** 2, and 3, with short term IV infusions on days 5 and 8 in R/R AML subjects. (eIV infusion may be implemented to FIH expansion groups based on emerging data).
- **MRD+ Group:** AMG 427 administered in short term IV infusions in MRD+ AML subjects.

At completion of the dose escalation cohorts, additional subjects (approximately 90 subjects, with approximately 40 subjects in the FIH cohorts and 50 subjects in the MRD+ groups) will be enrolled in a dose expansion cohort to gain further clinical experience, safety, and efficacy data in subjects with AMG 427.

3.1.1 Dose Escalation

The study will have 3 alternative dosing schedules:

- **(CLOSED)** Schedule A
  - D1/D5 or D1/D5/D12/D19 (dexamethasone prophylaxis)
- **(CLOSED)** Schedule B: Etanercept Substudy (R/R AML)
  - D1/D5 or D1/D5/D12/D19 (etanercept 2 days prior to each cycle).

    The etanercept substudy use**d** etanercept 2 days prior to infusion of each cycle D1, and if applicable, 2 days prior to infusion on D12. [redacted]
- **Schedule C** (Table 16 through Table 21): FIH, eIV (R/R AML)**;** MRD+ Group (MRD+ AML)
  - D1/D3/D5/D8 or D1/D3/D5/D8/D12/D19 (dexamethasone prophylaxis)

  Note:
  - The MRD+ group will use Schedule C for all cycle collections and Table 22 for addition**al** whole blood MRD collection**,** or Table 23**, as applicable.**

The initial cohort will begin with Schedule A and will receive 2 doses (1 each on D1 and D5). After reviewing the emerging PK, safety and efficacy data, the DLRT may recommend the administration of additional doses on D3 and D8, to comprise a 2-week cycle with doses on D1/D3/D5/D8 (Schedule C).

Additionally, if the following conditions are met, the DLRT may recommend the administration of 2 additional doses (D12 and D19):

- the 2-4 dose regimen (D1/D5 and/or D1/D3/D5/D8) is deemed safe and tolerable
- it is determined from the observed AMG 427 exposures that AMG 427 is rapidly cleared and/or distributed (ie, its observed half-life is much shorter than its predicted half-life)
- efficacy (based on clinical data and pharmacodynamic markers eg, clearance of $FLT3^+$ blasts in the blood and/or bone marrow) is observed but is not sustained and addition of D12 and D19 doses may improve the duration or depth of response

Once the DLRT recommends additional doses, all subsequent cohorts will be treated with a 4 or 6 dose regimen in each cycle. The additional doses (if applicable), may be at

the same dose as the preceding dose or may be at higher doses (dose step). A dose step is any dose that is higher for a given subject than the subject has previously received. Dose steps may occur at D3, D5, D8, D12, or D19 infusions.

Starting with an initial lower dose may improve tolerability of subsequently administered higher doses due to initial reduction of the bulk of blast cells, thereby improving efficacy. The DLRT will recommend an initial lower dose, which will not be higher than dose which triggered a DLT. For a schematic overview of the different dose step options see Figure 2 below.

Administration of a prophylactic steroid dose (8 mg IV dexamethasone) within 1 hour prior to start of AMG 427 dose on days 1, 3, 5, and 8 and prior to each dose step of AMG 427, to mitigate CRS, is mandatory. There is a ± 1-3 day window for dosing visits.

Other dose level(s) of dexamethasone may be evaluated as necessary.

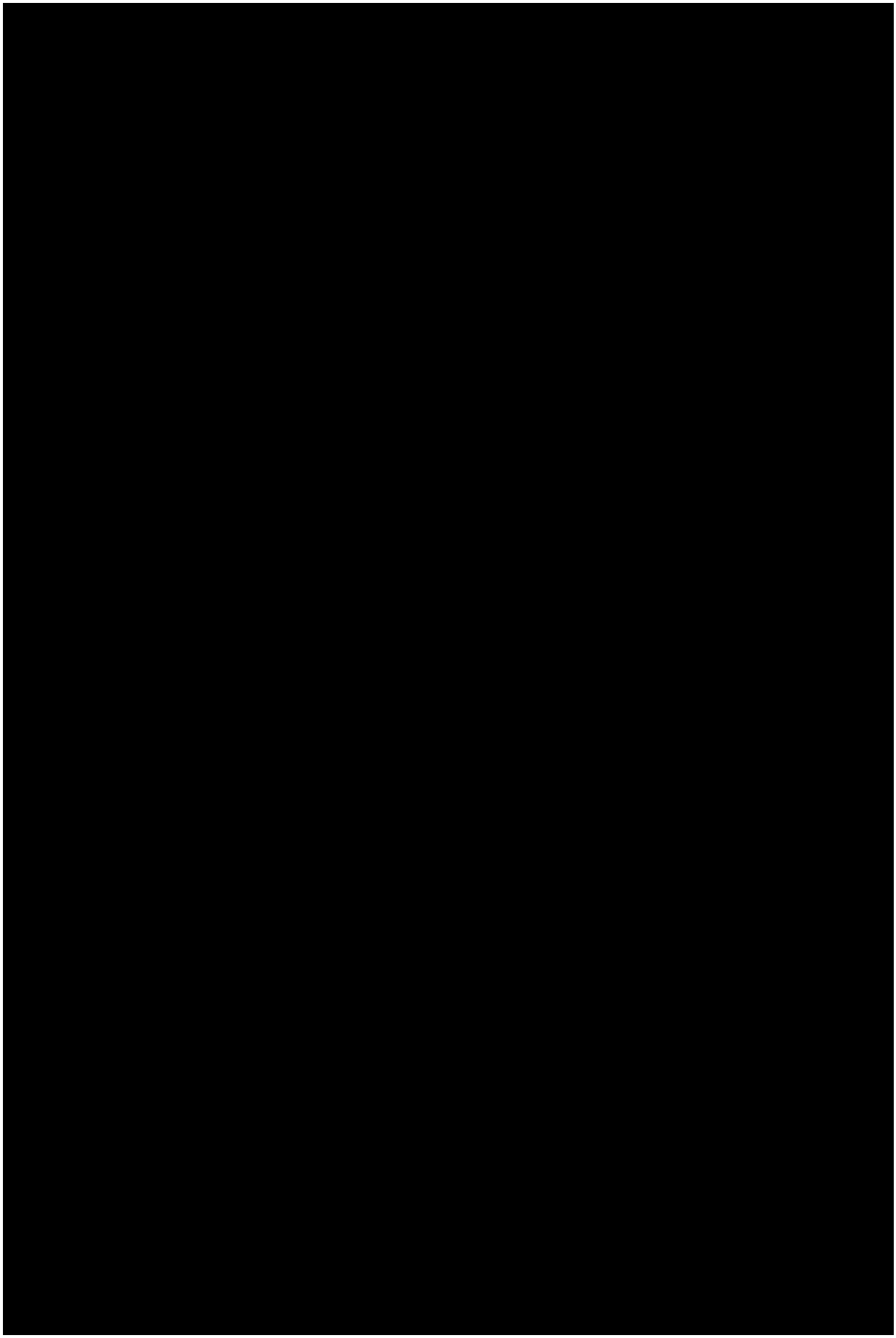
All other dosing rules, including dose limiting toxicities and treatment interruption, withholding, rechallenge, and permanent discontinuation apply as stated in Sections 6.2-6.6.

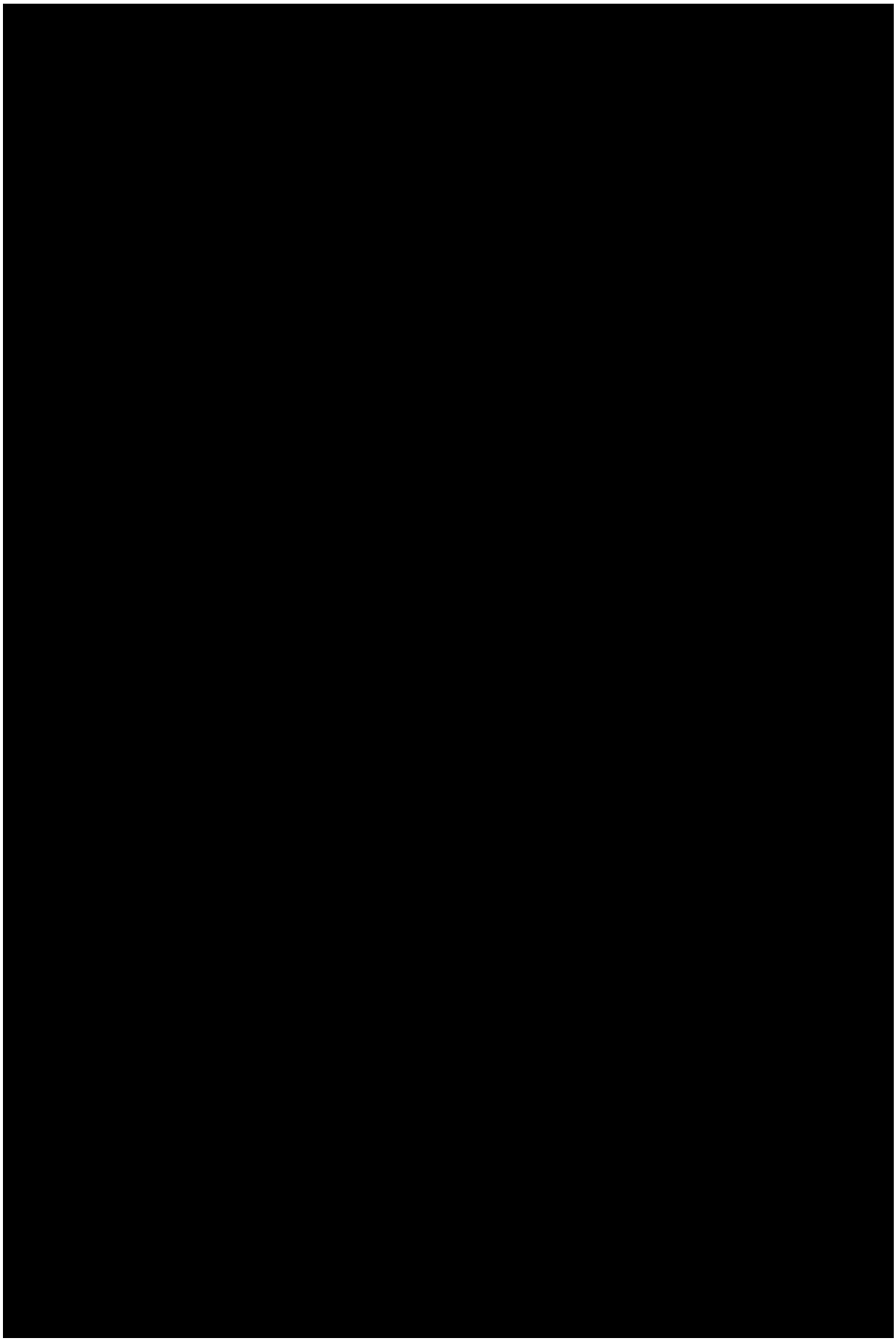
The estimate of the MTD(s), or the estimate of each MTD if step dosing is used, will use the BLRM design. Dose escalation will proceed using 2 parts: single subject cohorts and multiple subject cohorts.

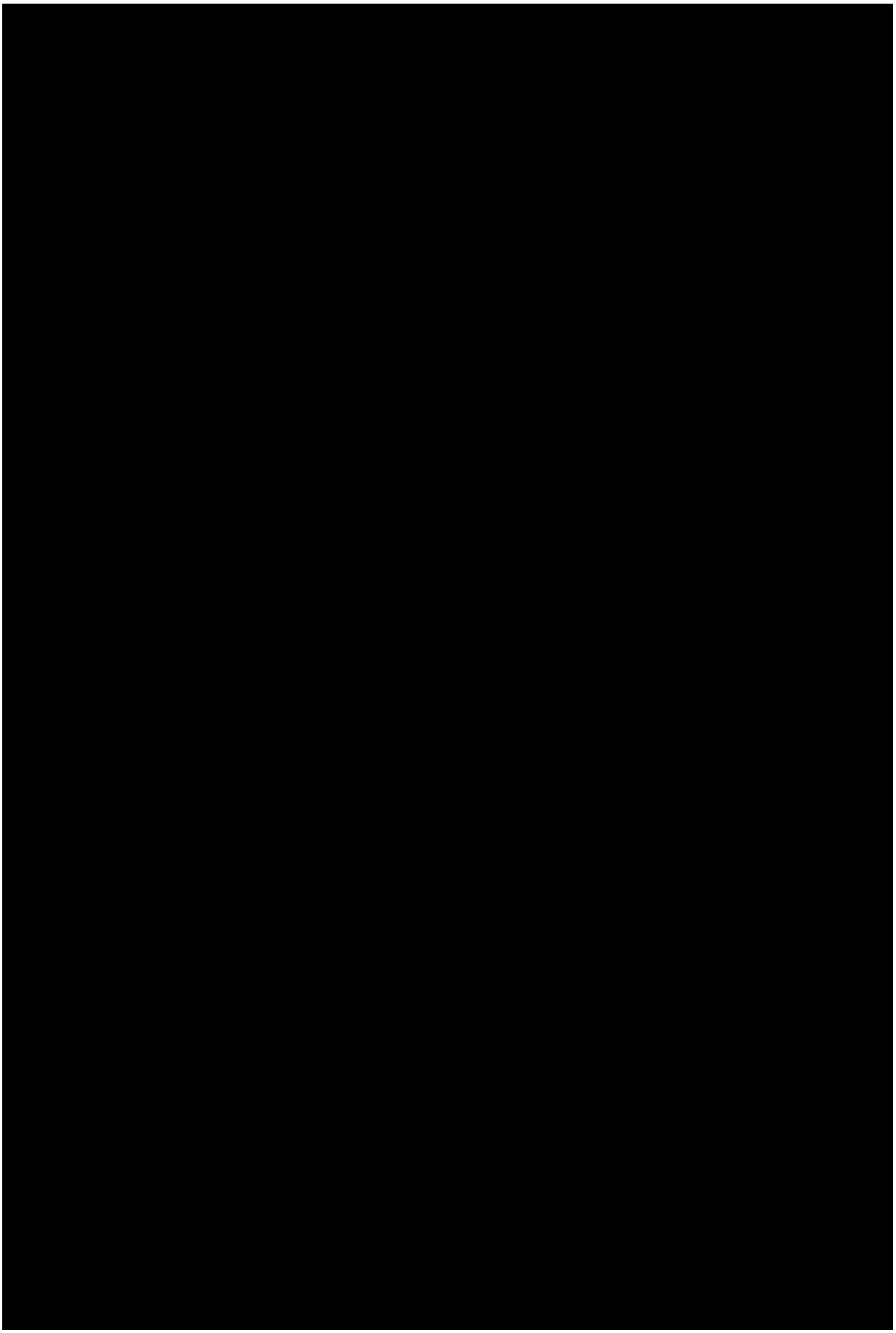
3.1.1.1 FIH Group

The FIH group will evaluate AMG 427 administered as a short-term IV infusion in adult subjects with R/R AML. In escalation, approximately 90 subjects with R/R AML will be a part of FIH cohorts [redacted] (Table 4). Approximately 25 subjects with R/R AML will receive etanercept for CRS prophylaxis 2 days prior to their cycle and follow guidance below. **The option for group extension may be available, either at sponsor discretion or if recommended by the DLRT based on the review of the emerging safety data. The sponsor will notify sites, if applicable, when the extended slots for a group are open for enrollment after DLRT has confirmed the dose level is safe.**

[redacted]







3.1.1.2 eIV Infusion Group

The eIV group will evaluate AMG 427 administered as an eIV infusion in approximately 10 subjects with R/R AML. The study will be conducted in dose escalation, to explore and identify if alternative dosing of AMG 427 leads to an improved benefit/risk profile. The option for group extension may be available, either at sponsor discretion or if recommended by the DLRT based on the review of the emerging safety data. The sponsor will notify sites, if applicable, when the extended slots for a group are open for enrollment after DLRT has confirmed the dose level is safe. If improvement is seen in the benefit/risk profile for these subjects, eIV administration may be implemented in the ongoing FIH (short IV) dose escalation cohorts, as well as expansion cohorts.

Utilizing Schedule C, the eIV study design will consist of eIV and short IV infusions of AMG 427 administered on days 1 **and** 2, 3, 5, and 8.

- Days 1 and 2 will consist of the D1 dose administered as an eIV infusion over 48 hours (approximately 12-hour IV bag changes).
- Day 3 will consist of the D3 dose administered as an eIV infusion over 24 hours (approximately 12-hour IV bag changes).
- The remaining 2 doses (D5 and D8) will be regular short IV infusions (approximately 90 minutes) on day 5 and day 8.

The first eIV group will start at **a** DLRT-approved dose level from the FIH group as described in Section 6.2.1.1.

Subsequent eIV cohorts will use the same dose levels as the FIH (short IV) cohorts (Table 4). Dose escalation may occur if the DLRT deems that the eIV cohorts demonstrate a better benefit/risk profile than the equivalent FIH (short IV) cohorts. All other study processes remain unchanged. Data will be continuously evaluated, and DLRT may recommend dose schedule/level changes based on emerging PK data.

3.1.1.2.1 Justification for eIV Investigational Product Dose

Based on preliminary population pharmacokinetic analyses, AMG 427 C_{max} is predicted to be approximately 40% lower with a delayed T_{max} if infused over a 72 hour period, relative to the same total dose administered using a 1 hour infusion. It is hypothesized that the use of eIV infusions over a 72 hour period may reduce the intensity and/or frequency of the symptoms associated with CRS, relative to the same total dose of AMG 427 infused over a 1 hour duration. The DLRT may recommend modifying the dose or modifying the C1D1 eIV infusion time up to 7 days based on emerging safety and PK data.

3.1.1.3 MRD+ Group

The MRD+ group will evaluate AMG 427 administered as short IV infusions (90 minutes) in approximately 10 adult subjects with MRD+ AML. **The option for group extension may be available, either at sponsor discretion or if recommended by the DLRT based on the review of the emerging safety data. The sponsor will notify sites, if applicable, when the extended slots for a group are open for enrollment after DLRT has confirmed the dose level is safe.**

In escalation, subjects will be enrolled and start at **a** dose level from the FIH group that has been cleared by the DLRT as safe and tolerable. For example, if DLRT approves as safe and tolerable, the following dosing regimen **for FIH short term IV**: day 1: [redacted] µg, day 3: [redacted] µg, day 5: [redacted] **µg, and day 8:** [redacted] µg, the first MRD**+** group 1 will be:

- Day 1: [redacted] µg
- Day 3: [redacted] µg
- Day 5: [redacted] µg
- Day 8: [redacted] µg

The escalation doses will follow Table 4 and all escalation rules and study procedures remain unchanged. If an MTD/RP2D is not determined after approximately 10 subjects, DLRT may recommend additional subjects for dose escalation, which will follow the dose escalation in Table 4.

3.1.2 Determination of Maximum Tolerated Dose

Dose escalation decisions will be made based on the recommendation of the BLRM model and the DLRT review after considering available safety, PK, PD, and efficacy data. The estimate of MTD will use the BLRM design. The model's estimated MTD dose is the dose with the highest probability of the target **toxicity probability interval (**TPI**)**, but with a less than 0.25 probability of an excessive or unacceptable TPI. The target TPI is (0.20, 0.33), and TPIs of (0.33, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. See Section 3.4 for replacement of subjects.

Dose escalations will continue until either of the following occurs:

- No DLTs are observed on study and
- A minimum of 6 subjects are treated at the highest planned dose level.
- DLTs are observed on study and
- BLRM repeats the recommendation of a dose level (minimum of 6 treated subjects), or

- A maximum of 90 subjects are enrolled. If fewer than 6 subjects are treated at the MTD, additional subjects beyond 90 may be enrolled to confirm safety and tolerability.

The MTD is defined as the highest dose level whose DLT rate has the highest probability of the target TPI, an excessive/unacceptable TPI of < 0.25, and a minimum of 6 subjects have been treated at the MTD.

Once the dose escalation phase has determined a final MTD **or optimal RP2D**, tocilizumab may be evaluated as an alternative prophylaxis to prevent/reduce the severity of CRS. A cohort of 3 subjects may be treated with AMG 427 at the final MTD dose level and a single dose of 8 mg/kg IV tocilizumab will be administered prior to the dose of AMG 427 replacing pretreatment with dexamethasone. If no DLTs are observed, 3 additional subjects will be included in this cohort. The use of tocilizumab may be further explored based on observed tolerability and other clinical and pharmacological data.

3.1.2.1 Maximum Tolerated Dose 1 (MTD1)

Dose escalation will proceed using 2 parts, single subject cohorts and multiple subject cohorts. In the single subject cohorts, single subjects will be enrolled at initial dose levels. When any pharmacologic activity (including, but not limited to, infusion reactions, cytokine release syndrome, decrease in peripheral blood blasts, or decrease in white blood cell count) is observed, the cohort size will be increased to multiple subject cohorts ($N = 2$ to 4 subjects). When the initial dose-limiting toxicity (DLT) is observed, the BLRM design will be used to guide dose level selection. After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive or unacceptable TPI. The actual dose selected at each dose decision may be at or below the model's recommended dose as recommended by the DLRT after considering all information.

The dose escalation will be stopped when any of the following occurs:

- A minimum of 6 subjects have been treated at the MTD1 level
- When the sample size reaches 120 subjects
- Or as recommended by the DLRT after considering available safety, PK, PD, and efficacy data

3.1.2.2 Maximum Tolerated Dose 2 (MTD2)

Dose escalation for the MTD2 following the initial dosing (MTD1) will proceed after MTD1 is determined and implements a dose step. The cohort for which a dose step will be implemented will start treatment for the first dose at the MTD1 assessed in the dose escalation for the first MTD. After this run-in dose, there may be a dose increase to the next higher dose as per the dosing schedule shown in Table 3 of the protocol. If this treatment schedule is tolerated, the following dose cohorts will continue to receive the run in (initial) dose at MTD1 to assess the MTD2. The target (second) dose will be increased until an MTD2 is reached. Testing of an MTD3 will be guided in the same way by the BLRM and the DLRT review after considering all information.

Subjects who complete the DLT period (see Section 6.2.1.4) may proceed to a higher dose level for the following treatment cycle once the next dose cohort has been deemed safe by the DLRT, after consultation with the sponsor, if the subject has:

- No DLT reported during or after the completion of the DLT period

See Section 7.2.2 for details on assessments applicable in case of intra-subject dose escalation. Dose limiting toxicities experienced by subjects after completing the DLT period will be considered in the BLRM design to account for any late onset toxicity.

Single Subject Cohorts

In the initial dose escalation cohorts, a single subject will be enrolled until any pharmacologic activity (including but not limited to infusion reaction, CRS, drop in white count) is noted. Evidence of pharmacologic activity will trigger multiple subject enrollment in the same and all subsequent cohorts. The initial dose levels are anticipated to be lower than the dose levels at which any clinical activity related to AMG 427 may be observed.

Multiple Subject Cohorts

Once multiple subject cohorts are triggered as described above, the same and subsequent cohorts will enroll 2 to 4 evaluable subjects based on BLRM output.

Time interval between Enrollment of Subjects in Each Cohort

There will be at least a 7-day (168-hour) interval between the start of treatment of the first and second subject in each cohort (ie, at the same dose and schedule). On day 7 of this interval, the site investigator will evaluate all available safety and laboratory data for the treated subject and confirm the occurrence/non-occurrence of a DLT to the sponsor. The sponsor will only be able to open enrollment for the next subject in the cohort after receipt of this confirmation. If deemed necessary, the 7-day interval may be extended until sufficient data are available to allow an assessment of the feasibility of treatment start of the next subject. In addition, there will be at least a 96-hour interval between the start of treatment of the second subject and all subsequent subjects in each cohort. Hence, no more than 3 subjects will be enrolled in 2 weeks.

Intra-subject dose escalation (ISDE)

A subject may receive a dose higher than what they received in the first cycle if:

- the next dose cohort has been deemed safe by the DLRT
- after consultation with the sponsor
- no DLT is reported during or after completion of the DLT period for that subject

- Subjects receiving low, subtherapeutic doses of AMG 427, such as subjects in the etanercept (Enbrel) substudy, may intra-subject dose escalate to a Dose Level Review Meeting (DLRM) approved dose immediately after cycle 1 if they have not experienced a DLT; the DLT window will remain 28 days (21 days if the subject shows disease progression)

3.1.3 Expansion Cohort

At completion of the dose escalation cohorts, approximately 90 additional subjects (approximately 40 R/R AML subjects in the FIH cohorts and 50 MRD+ AML subjects in the MRD+ cohorts) will be enrolled in dose expansion cohorts to gain further clinical experience, safety, and efficacy data in subjects with AMG 427. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. Once the preliminary MTD and R2PD are established, the FDA will be provided with brief interim results of the dose escalation phase.

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT once every 6th subject has at least completed their first treatment cycle plus 2 weeks or dropped out of treatment/study, whichever occurs earlier. The MTD will be further evaluated by applying BLRM using all available data, including data from subjects in the expansion phase. Ad hoc meetings may be convened any time in case of important safety events (see also Section 6.2.1.3).

Based on emerging safety data, the planned dose level and dose schedule may be modified during the conduct of the expansion phase. Additionally, enrollment to dose expansion will be paused and possibly terminated if safety stopping rules and/or efficacy futility rules are met (see Section 10.3 for details).

A final estimate of the MTD and RP2D using BLRM will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose escalation and the dose expansion cohorts. For definition of DLT-evaluable, see Section 6.2.1.3. Additional expansion cohorts testing alternative dose levels or biologic subsets may be considered by amendment.

The overall study design is described by a Study Design and Treatment Schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This study will be conducted at approximately 15 sites in the US, Australia, Canada, Japan, South Korea, and Germany. Additional countries or sites may be added if necessary.

Sites that do not enroll subjects into an open cohort within 6 months of site initiation may be closed or replaced.

3.3 Number of Subjects

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

It is anticipated that approximately 2**0**0 subjects will be enrolled in this study, with approximately 1**1**0 subjects enrolled in the dose escalation cohorts and 90 subjects in the dose expansion cohorts:

Dose escalation cohorts:

- FIH (R/R AML): approximately 90 subjects
  - **(CLOSED)** etanercept substudy (R/R AML): approximately 25 subjects
- eIV (R/R AML): approximately 10 subjects
- MRD Group (MRD+): approximately 10 subjects

Dose expansion cohorts:

- FIH (R/R AML): approximately 40 subjects
- MRD Group (MRD+): approximately 50 subjects

For ethical and operational reasons subjects who already are in the screening phase at the time of enrollment stop (end of expansion phase) will still be allowed to be treated. Therefore, an over running of subject recruitment might be possible.

Based on emerging data, additional subjects may be enrolled.

The rationale for the number of subjects is provided in Section 10.2.

3.4 Replacement of Subjects

Ineligible subjects (eg, subjects who were exposed to investigational product but post hoc were found to be ineligible) may be replaced. During dose escalation, subjects that are not DLT-evaluable will be replaced. See Section 6.2.1.3 for definition of DLT-evaluable subjects.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Dose escalation phase

It is anticipated that an individual subject enrolled in the dose escalation phase will participate in the study for up to 14 months. This includes a screening period lasting up to 14 days, a treatment period lasting approximately 10 to 12 months, and an SFU period lasting approximately 4 weeks after the last dose.

Dose expansion phase

Individual subjects enrolled in the dose expansion phase will participate in the study for up to about 2 years. This includes a screening period lasting up to 14 days, a treatment period lasting approximately 10 to 12 months, an SFU period lasting approximately 4 weeks after the last dose, and an LTFU period lasting up to 2 years after the first dose of AMG 427 (for subjects enrolled in the expansion phase only).

The actual duration for individual subjects will vary depending upon tolerability of AMG 427, evidence of clinical progression, and willingness to participate in the study.

After completion of a first cycle without a DLT, up to 11 additional treatment cycles can be administered as long as, in the judgment of the investigator, the subject is deriving benefit.

3.5.2 End of Study

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

The primary completion date is the date when the last subject either had the opportunity to receive up to 12 cycles of treatment or terminated the study early.

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

End of Study (For an Individual Subject):

An individual subject is considered to have completed the study if he/she has completed SFU visit for subjects enrolled in the dose escalation phase, or LTFU visit for subjects enrolled in the dose expansion phase as shown in the Schedule of Assessments (Section 7.1). The SFU visit should occur approximately 4 weeks (or up to 7 days thereafter) after the last dose of AMG 427 or prior to the initiation of other AML therapy, whichever occurs earlier.

End of study (EOS) for an individual subject is defined as the last day that protocol-specified procedures/assessments are conducted for the individual subject.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

101. Subject has provided informed consent prior to initiation of any study-specific activities/procedures

102. Subjects ≥ 18 years of age at the time of signing consent

103. For R/R AML subjects only, AML as defined by the WHO Classification (Appendix D) as persisting or recurring following 1 or more treatment courses (exceptions noted in exclusion criteria). Subjects must have failed treatment with, be intolerant to, or must not be candidates for available therapies for the treatment of R/R AML (not applicable to MRD+ subjects)

104. For R/R AML subjects only, myeloblasts ≥ 5% in bone marrow, as confirmed by immunophenotype by flow cytometry (not applicable to MRD+ subjects)

105. Eastern Cooperative Oncology Group (ECOG, Appendix F) Performance Status of ≤ 2

106. Renal function as follows:

- serum creatinine < 2.0 mg/dL (176.84 μmol/L)
- estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2

107. Hepatic function as follows:

- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN)
- bilirubin ≤ 1.5 x ULN (unless considered due to Gilbert's syndrome or hemolysis)

108. **(CLOSED)** Etanercept (Enbrel) substudy only:

No active tuberculosis in the setting of anti-TNF therapy

National guidelines should be followed for appropriate tuberculosis screening in the setting of anti-TNF therapy, including a minimum of:

- Subject has a negative test for tuberculosis during screening defined as either:
  - Negative purified protein derivative (PPD) (< 5 mm induration at 48 to 72 hours after test is placed) OR
  - Negative Quantiferon test

Subjects with positive PPD and a history of bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test.

Subjects with a positive PPD test (without a history of bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:

- no symptoms, per tuberculosis worksheet provided by Amgen
- documented history of a completed course of adequate treatment or prophylaxis (per local standard of care) prior to the start of investigational product
- no known exposure to a case of active tuberculosis after most recent prophylaxis
- no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product

109. For the MRD+ Group, AML subjects in any CR/CRh/CRi:

- with detectable measurable/MRD as assessed by local institution

  [redacted]

  The MRD assessment must have been performed within 3 months of enrollment.
- not eligible for allogenic HSCT per investigator assessment, lacking a donor, or declining the procedure

Subject may have received any induction and consolidation/maintenance regimens, including cytotoxic agents, hypomethylating agents, transplant, or other therapeutics, to achieve CR/CRh/CRi, prior to screening.

4.2 Exclusion Criteria

201. Patients with acute promyelocytic leukemia (APML)

202. Active extramedullary AML in the central nervous system (CNS)

203. Known hypersensitivity to immunoglobulins

204. White blood cells (WBC) > 15,000 cells/mcL (15 cells x 10^9/L) at screening (hydroxyurea is permitted to enable eligibility)

205. Subjects with a prior or concurrent malignancy whose natural history or treatment is anticipated to interfere with the safety or efficacy assessment of the investigational regimen.

Exception: Subjects with prior or concurrent malignancy not anticipated to interfere with the safety or efficacy assessment of the investigational regimen may be included only after discussion with the Amgen Medical Monitor.

206. For R/R AML subjects only, autologous HSCT within 6 weeks prior to start of AMG 427 treatment (MRD+ subjects may be enrolled only after discussion with sponsor)

207. For R/R AML subjects only, allogeneic HSCT within 3 months prior to start of AMG 427 treatment (MRD+ subjects may be enrolled only after discussion with sponsor)

208. Any graft-versus-host disease requiring systemic therapy with immunomodulators

209. History or evidence of significant cardiovascular risk including any of the following: symptomatic congestive heart failure, unstable angina, clinically significant arrhythmias (eg, ventricular fibrillation, ventricular tachycardia etc.), recent coronary angioplasty, intra-cardiac defibrillators or any clinically relevant concurrent disorder that may pose a risk to subject safety or interfere with study evaluation, procedures, or completion

210. History of arterial thrombosis (eg, stroke or transient ischemic attack) in the past 3 months

211. Active infection requiring intravenous antibiotics within 1 week of study enrollment (day 1). Antibiotics may be administered for prophylaxis as per institutional standards up to and after enrollment.

212. Known positive test for human immunodeficiency virus (HIV)

213. Positive for hepatitis B surface antigen (HepBsAg)

214. Positive for hepatitis C or chronic hepatitis C

    Possible exceptions: acute hepatitis C and completely cleared of the virus (demonstrated by negative viral load), chronic hepatitis C with undetectable viral load defined by sustained virologic response 24 weeks (SVR24) after completion of anti-hepatitis C treatment.

215. Live vaccination(s) within 4 weeks before the start of AMG 427 treatment on day 1, during treatment, and until the end of the last study dose

216. Unresolved toxicities from prior antitumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 grade 1 (with the exception of myelosuppression, eg, neutropenia, anemia, thrombocytopenia), or to levels dictated in the eligibility criteria with the exception of alopecia or toxicities from prior antitumor therapy that are considered irreversible (defined as having been present and stable for $>$ 2 months) which may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor

217. Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy such as FLT3 inhibitors, or investigational agent) within 14 days of day 1

    - Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed until start of investigational product treatment
    - Exception: antitumor therapies with short half-lives only require passing of 5 half-lives from last dose, and after discussion with sponsor

218. Treatment with systemic immune modulators including, but not limited to, non-topical systemic corticosteroids, cyclosporine, and tacrolimus within 2 weeks before enrollment (day 1)

- Exception: physiologic replacement steroids or steroids for treatment of transfusion/hypersensitivity reactions

219. Prior treatment with a FLT3 targeting CAR-T

220. Major surgery within 28 days of study day 1 with the exception of biopsy and insertion of central venous catheter

221. History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen medical monitor would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

222. Males and females of reproductive potential who are unwilling to practice a highly effective method(s) of birth control while on study through 4 weeks after receiving the last dose of study drug. Acceptable methods of highly effective birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (men) in combination with hormonal birth control or intrauterine device (IUD) (women)

223. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 4 weeks after receiving the last dose of study drug

224. Females with a positive pregnancy test

225. Females planning to become pregnant while on study through 4 weeks after receiving the last dose of study drug

226. Subjects likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge

227. History of multiple sclerosis or any other demyelinating disease

228. Active hepatitis secondary to alcoholic hepatitis or nonalcoholic steatohepatitis

229. History or evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection unless agreed upon with Medical Monitor and meeting the following criteria:

- **Negative test for SARS-CoV-2 RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) within 72 hours of first dose of investigational product**
- **No acute symptoms of coronavirus disease 2019 (COVID-19) disease within 10 days prior to first dose of investigational product (counted from day of positive test for asymptomatic subjects)**

5. SUBJECT ENROLLMENT

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

activities/procedures. A subject is considered enrolled when they have met all the eligibility criteria. The Investigator is to document the enrollment decision and date in the subject's medical record.

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 528). The next 5 digits will represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at site 66001 will receive the number [redacted], and the second subject at the same site will receive the number [redacted]

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Subjects who do not meet the eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period. With the exception of hepatitis serology and bone marrow assessments, re-screened subjects who are re-consented will repeat all screening procedures. See Section 7.2.1 for assessments during re-screening. Subjects who are deemed ineligible will be documented as screen failures.

Subjects may be eligible to begin treatment once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to the sponsor or designee.

5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects. In the initial dose escalation cohorts, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active. Evidence of

pharmacologic activity will trigger multiple subject enrollment in the same and all subsequent cohorts. Enrollment will be performed according to the BLRM design (see Section 3.1 for details) from the first multiple subject cohort onwards. Each multiple subject cohort will enroll up to 4 evaluable subjects.

At completion of the dose escalation cohorts, additional subjects, approximately 90 (FIH: N = 40, MRD+: N = 50) will be enrolled in a dose expansion cohorts to gain further clinical experience, safety and efficacy data in subjects with AMG 427. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts.

6. TREATMENT PROCEDURES

6.1 Classification of Product

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

The Amgen investigational product used in this study is AMG 427.

In this study (starting with the etanercept (Enbrel) substudy [redacted]), etanercept (Enbrel® [investigational use of a marketed product]) will be used (US only) prophylactically to mitigate signs, symptoms, and severity of CRS. Etanercept is not FDA-approved for the disease/condition being studied. Etanercept will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

6.2 Investigational Product

The investigational product will be administered at the research facility by a qualified staff member.

A physician or nurse trained in emergency procedures must be available when the infusion of investigational product is started for immediate intervention in case of complications.

6.2.1 Amgen Investigational Product AMG 427

AMG 427 will be manufactured and packaged by Amgen Inc., or its agents, and distributed using Amgen or its agents' clinical study drug distribution procedures.

AMG 427 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile Water for Injection (WFI). After reconstitution with 1.2 mL of sterile WFI, the 1 mg/mL AMG 427 drug product is

formulated with [redacted] mM glutamic acid, [redacted]% (w/v) sucrose, and [redacted]% (w/v) polysorbate 80, pH [redacted] The final container is a single-use, 6R glass vial and contains a target extractable amount of 1 mg AMG 427.

The intravenous solution stabilizer (IVSS) is intended for pre-treatment of IV bags prior to dilution of AMG 427 drug product. The IVSS is supplied as a sterile solution in a 10-cc glass vial containing 10 mL deliverable product. The IVSS does not contain an active pharmaceutical ingredient and is a buffered, preservative-free solution ([redacted] mM citric acid, [redacted] M lysine hydrochloride, [redacted]% (w/v) polysorbate 80, pH [redacted]).

6.2.1.1 Dosage, Administration, and Schedule

AMG 427 may be administered as short-term IV infusions, delivered using infusion pumps (for the higher doses) and syringe pumps (for the lower doses), respectively, which are both approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 427 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. An IV flush bag will be connected to the IV infusion line after AMG 427 dose infusion is completed to administer a controlled rate post-infusion flush. The drug will be administered as short-term IV infusions (approximately 90 minutes) on D1, D3 (if applicable), D5, and D8 (if applicable) of each treatment cycle followed by an infusion-free interval prior to the start of the following treatment cycle. AMG 427 solution will be prepared in bags for short or eIV infusion and delivered through infusion lines.

The first eIV group will start at **a** DLRT-approved dose level from the FIH group, eg, if DLRT approves as safe and tolerable, the following dosing regimen will be administered:

- Days 1 and 2: eIV of [redacted] μg (over approximately 48 hours, with approximately 12-hour bag changes)
- Day 3: eIV of [redacted] μg (over approximately 24 hours, with approximately 12-hour bag changes)
- Day 5: short IV of [redacted] μg (over approximately 90 minutes)
- Day 8: short IV of [redacted] μg (over approximately 90 minutes)

Subsequent eIV cohorts will use the same dose levels as the FIH (short IV) cohorts (Table 4).

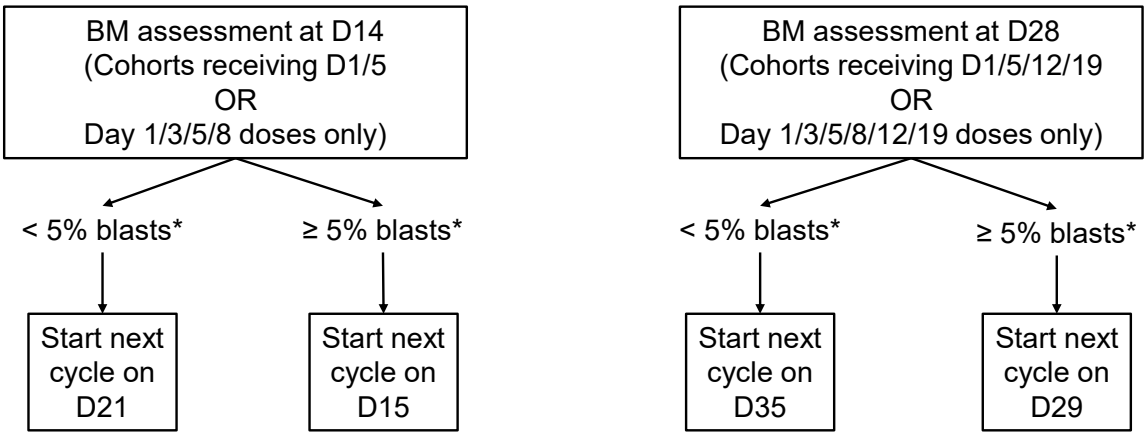
Two additional infusions, on D12 and D19 of each cycle, may be implemented by DLRM recommendation. The infusion-free interval will have a duration of 1 to 5 weeks (depending on treatment response), but may be extended to up to 7 weeks in case of

prolonged marrow aplasia and aleukemic cytopenias after consultation with the sponsor. It may also be extended for up to 3 days from the planned duration if necessary for logistical reasons. For further details on planned dosing and infusion details can be provided if needed, please also see Section 3.1.

The planned dose levels for the dose escalation cohorts are: [redacted] µg. The MTD or highest tested dose (or doses, in case of dose step) will be administered in the dose-expansion cohort.

After completion of a first cycle without DLT, up to 11 additional treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit.

The duration of the infusion-free interval between the last infusion of a treatment cycle and the D1 infusion of the subsequent cycle is dependent on treatment response and recovery of blood counts (see below and Figure 4 for details). It may also be extended for up to 3 days from the planned duration, if necessary, for logistical reasons. The DLRT may recommend on changes of the duration of the infusion-free interval for future cohorts after evaluation of PK data.



The infusion-free interval may be extended up to a maximum of 7 weeks in case of insufficient recovery of peripheral blood counts in the absence of active AML (neutrophils > 500/µL, platelets > 20 000/µL)
AML = acute myeloid leukemia; BM = bone marrow; D = day
* Myeloblasts must be confirmed by flow-cytometry based immunophenotype

The infusion-free interval may be extended up to a maximum of 7 weeks in case of insufficient recovery of peripheral blood counts back to baseline or neutrophils > 500/µL,

platelets $>$ 20 000/μL without transfusion in the absence of active AML, after consultation with the sponsor. In case the infusion-free interval is extended to 7 weeks, a bone marrow assessment is recommended 5 weeks after the last infusion of a cycle. In case this assessment shows leukemic infiltration of the bone marrow ($\geq$ 5% blasts), treatment should be resumed immediately even if peripheral blood counts have not yet recovered at this time point.

Hospitalization

Subjects will be hospitalized for a minimum of 8 or 11 days from the start of the first dose in cycle 1 (ie, until at least 72 hours after D5 or D8, depending on schedule) and for a minimum of 72 hours following D12 and D19 doses in cycle 1. If the subject receives a second subsequent cycle of AMG 427 at the same dose, hospitalization will be for a minimum of 8 or 11 days from start of the day 1 dose (ie, at least 72 hours after D5 or D8, depending on schedule). Hospitalization following D12 and D19 doses in cycle 2 and onwards will be at the discretion of the treating physician. For subjects receiving $>$ 2 cycles, hospitalization for cycle 3 onwards for all doses will be at the treating physician's discretion.

Additionally, subjects will be hospitalized for a minimum of 72 hours under the following circumstances:

- after each new dose step, if applicable
- after dose increase in case of intra-subject dose escalation
- after re-start of treatment after an interruption due to adverse event

Subjects can be hospitalized for a longer time period at the discretion of the investigator.

Hospitalization requirements may be reduced for subjects enrolled in the dose expansion phase based on cumulative safety and tolerability data from the dose escalation phase, by DLRT recommendation.

A nurse trained in emergency procedures or a physician must be available when the dose of AMG 427 is started for immediate intervention in case of complications. The hospitalization period may be extended at the discretion of the investigator. During hospitalization periods, an immediately accessible emergency room with resuscitation equipment must be available.

Prior to hospital discharge, vital signs will be measured in order to detect possible signs and symptoms of CRS. If required for logistical reasons (eg, long travel times), subjects may be hospitalized the day before start of dosing (eg, day -1).

The start time of dose should be chosen carefully so as to avoid any interference or inconvenience with time points of safety assessments or PK/PD measurements. The site should record any unscheduled interruption of a dose on the electronic case report form (eCRF), and provide the start and stop date/time of the infusion.

AMG 427 should be administered through a central venous access at a constant flow rate. The drug should not be administered as a bolus. In the event that administration through a central venous access is not possible, AMG 427 may be administered through a peripheral venous line.

The concentration, quantity administered, start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's eCRF.

6.2.1.2 Overdose

The effects of overdose of this product are not known. The administered AMG 427 dose may be up to 10% lower or higher than specified in the protocol due to pump variation and will not be considered an overdose. A dose of up to 10% higher than the intended dose may not require specific intervention.

In any case of overdose, consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also strongly recommended even if there are no adverse events, in order to discuss further management of the subject. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event(s) should be recorded/reported per Section 9.2.1.2.

A dose of > 10% higher than the intended AMG 427 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.2.1.2.

6.2.1.3 Dose-cohort Study Escalation and Stopping Rules, Dose Limiting Toxicities (DLTs)

A DLT will be defined as any of the events described below occurring in a subject during the DLT window. The DLT window will start on D1 (start of the administration of the first dose) and last for 28 days for all cohorts. Any adverse event occurring outside the DLT window that is determined by the investigator to be possibly related to the investigational product, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous

recommendation by the DLRT after review of the adverse event and all available safety data.

DLT Evaluation

A subject will be DLT-evaluable if the subject has received the doses planned for the respective cohort, and completed the DLT window of 28 days for all cohorts. The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent (eg, in case of neutropenia).

A subject is not DLT-evaluable if he/she drops out before completion of the DLT window for reasons other than a DLT; exception: if a subject has received the planned doses in cycle 1 and drops out within 1 week of the completion of the DLT period due to progressive disease, that subject will be considered DLT-evaluable and will not be replaced. All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRM recommendations. A DLT will be defined as any of the events described below occurring in a subject during the DLT window unless clearly attributable to causes other than AMG 427 treatment. The CTCAE version 4.0 (see Appendix A) will be used to assess toxicities/adverse events with the exception of CRS **(s**ee Table 6 for grading criteria of CRS**) and immune-effector associated neurotoxicity syndrome (ICANS) (see Table 8 for grading criteria of ICANS)**.

Events to be considered as DLTs and exceptions are listed below:

- Cases of drug-induced liver injury confirmed by Hy's Law criteria
- Any treatment-related death
- Grade 2 or 3 CRS meeting any of the criteria listed below:
  - Grade 2 CRS that does not resolve, with or without intervention, to ≤ grade 1 within 7 days will be considered a DLT
  - Grade 3 CRS that does not resolve, with or without intervention, to ≤ grade 2 within 5 days, or ≤ grade 1 within 7 days, will be considered a DLT
  - Grade 3 CRS reported at the initial run-in dose (ie, at MTD1; applicable only after MTD1 has been defined) will be considered a DLT
  - Two separate events of grade 3 CRS
- Grade 4 CRS/infusion reactions occurring during AMG 427 treatment, immediately stop the infusion. Permanently discontinue AMG 427 therapy.
- Grade 3−5 non-hematologic toxicity not clearly resulting from the underlying leukemia EXCEPT:
  - alopecia
  - grade 3 rash
  - grade 3 fatigue, asthenia, fever, anorexia, or constipation

  - grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization
  - infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia
  - grade 3 infusion reaction including CRS, if successfully managed and which resolves within 12 hours
  - grade 3 TLS if it is successfully managed clinically and resolves within 7 days without end-organ damage.
- Grade 4 neutropenia that persists beyond 42 days in the absence of leukemia
- Laboratory parameters ≥ grade 3, not considered clinically relevant, and improved to ≤ grade 2 within 72 hours, will not be considered DLT's. Laboratory parameters with long half-lives, ie, ALT, GGT, ALP, and lipase, will likewise not be considered DLT's if they are not considered clinically relevant, and improve to grade ≤ 2 within 7 days.
- Grade 3 transaminitis (per CTCAE criteria) reported for subjects with grade 2 CRS (per Lee et al, 201**9** criteria) will not be reported as a DLT if there is improvement to CRS ≤ grade 1 within 7 days.

The dosing schedule is described by a schema in Figure 2.

See Section 3.1 for description of dose escalation and stopping rules and Section 3.4 for description of replacement of subjects.

Subjects who have experienced a DLT at a certain dose level may continue to receive AMG427 at a lower dose, if AMG 427 has shown a potential for benefit in the specified subject, the subject's adverse events have reduced to grade 2 or lower, and after discussion with the Amgen Medical Monitor.

6.2.1.4 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Treatment Interruption

Significant events attributed to the drug or infusion may require treatment interruption.

Note: The definition of treatment interruption may include interruption of infusion or delay of the subsequent dose.

Events leading to treatment interruption may include:

- The subject experiences a grade ≥ 3 adverse event related to the infusion/drug
- Technical problem with the syringe/infusion pump/syringe pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

Treatment Interruption and Re-Start in Case of Adverse Events During the Infusion

Treatment must be modified for any clinically relevant (as determined by investigator) adverse events that occur during the infusion and are related to investigational product, as follows:

- grade 2 adverse event: **Prior** to **next dose, adverse event must resolve to grade 1 or less for at least 24 hours, including isolated lab abnormalities and organ toxicity labs**
- grade 3 adverse event: Interrupt the infusion until the adverse event is grade ≤ 1 **for at least 24 hours prior to the next dose of AMG 427**. Restart at the same dose if interruption is ≤ 72 hours. If interruption is > 72 hours, restart at a lower dose (last safe dose as **recommended** by DLR**T or a lower dose**). If the adverse event is a DLT, follow Section 6.2.1.3 for management of DLT.
  - **Subjects who experience CRS grade 3 should have next dose delayed until CRS resolves to grade ≤ 1 for at least 24 hours prior to the next dose of AMG 427 (including isolated lab abnormalities and organ toxicity labs, except for liver function tests, which must resolve to grade 2 or less), and should have next dose(s) reduced by one-half or more, if given on scheduled day (please consult with the study medical monitor).**
- grade 4 adverse events during the infusion: Permanently discontinue the investigational product

The Amgen medical monitor has to be consulted prior to a planned re-start.

In case of a dose reduction, re-escalation to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated. An intermediate dose level may be administered prior to stepping up to the target dose after consultation with the Amgen medical monitor.

The subject should be hospitalized for at least 72 hours after re-start of the infusion.

If possible, the number of infusions at the target dose in a cycle should sum up to the planned number of infusions. In this case, the cycle would still be DLT-evaluable.

Permanent Discontinuation

A subject will permanently discontinue treatment with investigational product in the event of:

- dose-limiting or other unmanageable toxicity
  - except subjects who have experienced a DLT at a certain dose level may continue to receive AMG427 at a lower dose, if AMG 427 has shown efficacy in the specified subject, and the subject's adverse events have reduced to grade 2 or lower, and after discussion with the Amgen Medical Monitor.
- grade 4 CRS
- grade 2 or 3 CRS meeting any of the criteria listed below:

  - grade 2 or 3 CRS that does not improve to ≤ grade 1 within 7 days
  - grade 3 CRS that does not improve to ≤ grade 2 within 5 days
  - grade 3 CRS at the initial run-in dose for a cycle (ie, at the MTD1) (for cohorts with dose step only)
  - If a subject experiences 2 separate grade 3 CRS events
- disease progression as defined by revised IWG response criteria (Appendix E)
- withdrawal of subject's consent to treatment
- subject or investigator not compliant with the study protocol
- occurrence or progression of a medical condition, which in the opinion of the investigator, should preclude further participation of the subject in the study
- a treatment interruption of more than 21 days due to an adverse event not clearly related to the underlying disease (except neutropenia)
- occurrence of a CNS-related adverse event considered related to AMG 427 by the investigator and meeting 1 or more of the following criteria:
  - more than 1 seizure
  - a CNS-related adverse event grade 4
  - a CNS-related adverse event leading to treatment interruption that needed more than 1 week to resolve to grade ≤ 1
- graft-versus-host disease
- investigator's decision that a change of therapy (including immediate HSCT) is in the subject's best interest

Females who become pregnant while on study through 4 weeks after receiving the last dose of study drug will not receive subsequent scheduled doses and will be followed for safety until the end of study visit.

Males on study through 4 weeks after receiving the last dose of study drug must practice sexual abstinence or use a condom while on study through 4 weeks after receiving the last dose of study drug.

All reasons for treatment discontinuation should be clearly and concisely documented in the eCRF. If a subject has not continued to present for study visits, the investigator should determine the reason and circumstances as completely and accurately as possible.

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the end of treatment (EOT) and SFU visits. These data should be recorded, as they comprise an essential evaluation that should be performed prior to discharging any subject from the study and to allow for the evaluation of the study endpoints.

6.3 Other Protocol-required Therapies

All other protocol-required and recommended therapies, including corticosteroids, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these therapies.

Oxygen: Oxygen administration as a supportive measure is permitted during study treatment.

Hydroxyurea: Hydroxyurea may be permitted according to standard practice prior to the first cycle of investigational product treatment for subjects with high WBC (> 15,000 cells/μL or 15 cells x 10^9/L). Administration of hydroxyurea after the start of AMG 427 may be permitted after discussion with the Amgen medical monitor.

Dexamethasone: Premedication with dexamethasone is required for every cycle before infusion of AMG 427 dosing and prior to each dose step of AMG 427 to mitigate the risk of CRS. When dosed, dexamethasone should be administered as a single IV dose (8 mg) within 1 hour of start of infusion.

Methylprednisolone: may also be utilized as per Table 6 to treat CRS, per institutional practice.

Tocilizumab: Tocilizumab will be used to treat cytokine release syndrome (**Actemra®** USPI**, 2021**), as described in Table 6. In addition, use of prophylactic tocilizumab to mitigate CRS will be tested in a cohort of subjects once final MTD has been established, as described in Section 3.1.2. For administration of dexamethasone and tocilizumab after occurrence of CRS, follow guidance in Section 6.6. Additional details regarding these protocol-required therapies are provided. **Sites are required to have tocilizumab or siltuximab (if tocilizumab not available) on site for potential treatment of CRS (Sylvant™ USPI, 2015). If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of cytokine release syndrome, following the criteria outlined in Table 7. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant™ USPI, 2015), and the CARTOX Working Group Guidelines for CRS management (Neelapu et al, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 427. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after**

siltuximab. A subgroup analysis for those treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

Anakinra: The interleukin-1 receptor (IL-1R) blocker/inhibitor will be used for symptoms of CRS-related ICANS as per Table 8. In preclinical models, Anakinra has shown to abolish both CRS and neurotoxicity, resulting in substantially extended leukemia-free survival (Norelli et al, 2018). Interleukin-1 receptor inhibitor has been found to be useful in managing CRS related acute respiratory distress syndrome and ICANS/neurotoxicity (Morris et al, 2021).

(CLOSED) Etanercept: Etanercept will be used prophylactically to mitigate signs/symptoms/severity of cytokine release syndrome. [redacted].

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

6.4.1 Criteria for Permanent Withholding of AMG 427 due to Potential Hepatotoxicity

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

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

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

AND

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

AND

- No significant elevation of ALP (≤ 2x ULN)

- No other cause for the combination of the above laboratory abnormalities is immediately apparent including pre-existing or acute liver disease. Important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
  - exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-1 antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.4.2 Criteria for Conditional Withholding of AMG 427 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 427 outlined above and have no underlying liver disease and eligibility criteria requiring normal transaminases and TBIL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:
  - Any AST or ALT elevation: $>$ 8 x ULN at any time
  - Any AST or ALT elevation: $>$ 5 x ULN but $<$ 8 x ULN for $\geq$ 2 weeks
  - Any AST or ALT elevation: $>$ 5 x ULN but $<$ 8 x ULN and unable to adhere to enhanced monitoring schedule
  - Any AST or ALT elevation: $>$ 3 x ULN with clinical signs or symptoms which are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, or jaundice).
- OR: TBIL $>$ 3 x ULN at any time
- OR: ALP $>$ 8 x ULN at any time

AMG 427 should be withheld pending investigation into alternative causes of the laboratory elevations. If the investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBIL level is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

Discontinuation of the product should be considered and the decision to re-challenge should be discussed with the Amgen medical monitor before re-initiating treatment with investigational product.

6.4.3 Criteria for Rechallenge of AMG 427 After Potential Hepatotoxicity

If signs or symptoms recur with rechallenge, then the investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should not be rechallenged.

6.5 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9. COVID-19 vaccine administration (if applicable) should be captured in the concomitant medications.

Concomitant therapies are to be collected from informed consent, through the SFU or LTFU, as applicable. For all concomitant therapies **including vaccines,** collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.5.1 Vaccines

Every effort should be made to fully vaccinate subjects prior to 14 days from first dose of AMG 427. The use of vaccines except live vaccines will be allowed during therapy per regional and institutional standard of care. However, SARS-CoV-2 vaccinations should be avoided during screening (within a minimum of 14 days from first dose of AMG 427) and should be also avoided in the first treatment cycle for better assessment of safety parameters. Throughout the trial, SARS-CoV-2 vaccination should be avoided within 3 days after the administration of AMG 427. In the event where a subject requires steroids for treatment of adverse events, vaccination should be avoided while on steroids.

Table 5. Management of COVID-19

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 disease				
Asymptomatic	Interruption required until at least 10 days since positive SARS-CoV-2 test UNLESS patient previously fully vaccinated against SARS-CoV-2. If patient previously vaccinated and tests positive, then discuss with Medical Monitor.	Follow local guidelines and standard of care for COVID-19 treatment and isolation Contact Amgen Medical Monitor within 1 business day to ensure appropriate documentation & management of study activities	• Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided: ○ There are no new findings on physical exam related to SARS-CoV-2, AND ○ Subject tests negative for SARS-CoV-2 by RT-PCR, OR ○ If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, or If subject initially tests positive in the setting of prior COVID vaccination, resume investigational product only after discussion with patient and reassessment of individual risk/benefit • Consider chest imaging, EKG, ECHO, and cardiology assessment • Consider hospitalization for re-start of investigational product based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Premedication and assessments: follow guidance in schedule of assessment tables	Immediately stop the infusion (if applicable) and permanently discontinue investigational product therapy IF: Subject required treatment interruption greater than 28 days and upon discussion with Amgen Medical Monitor the decision is made to permanently discontinue treatment OR Initial benefit/risk assessment for individual patient is not maintained any longer

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Footnotes defined on next page of the table

Table 5. Management of COVID-19

Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
SARS-CoV-2 infection and COVID-19 disease				
Symptomatic	Interruption required until at least 10 days since complete resolution of acute symptoms	Interruption required until at least 10 days since complete resolution of acute symptoms	• Re-start possible upon agreement between Investigator and Amgen Medical Monitor provided: ○ There are no new findings on physical exam and chest imaging, related to SARS-CoV-2, ○ Subject tests negative for SARS-CoV-2 by RT-PCR, OR ○ If subject continues to test positive for SARS-CoV-2 more than 10 days after initial positive test, resume investigational product only after discussion with patient and reassessment of individual risk/benefit • Consider chest imaging, EKG, ECHO, and cardiology assessment • Consider hospitalization for re-start of investigational product based on length of treatment interruption, risk of CRS at restart, and amount of time since patient was last treated • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Premedication and assessments: follow guidance in schedule of assessment tables	Immediately stop the infusion (if applicable) and permanently discontinue investigational product therapy IF Subject required treatment interruption greater than 28 days due to severe or life-threatening COVID-19 OR Initial benefit/risk assessment for individual patient is not maintained any longer

COVID-19 = coronavirus-19; CRS = cytokine release syndrome; ECHO = echocardiography; EKG = electrocardiogram; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

6.6 Specific Recommendations for Cytokine Release Syndrome, Immune-effector Cell-associated Neurotoxicity Syndrome,Tumor Lysis Syndrome and Infection Prophylaxis

Cytokine Release Syndrome

Cytokine release syndrome is clinically defined and may have various manifestations. There are no established diagnostic criteria. Signs and symptoms of CRS may include:

- Constitutional – fever, rigors, fatigue, malaise
- Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure
- Respiratory – dyspnea, tachypnea, hypoxemia
- Cardiovascular – tachycardia, hypotension
- Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia
- Hematology – bleeding, hypofibrinogenemia, elevated D-dimer
- Skin – rash

Cytokine release is an anticipated consequence of T cell engagement induced by AMG 427. Cytokine release syndrome, including serious events **and a fatal event**, has been reported **in subjects** receiving AMG 427 in the clinical trial. Subjects may be at an increased risk for CRS during the first few days following the initial dose of AMG 427 and after a dose step. **More severe cases of CRS and/or ICANS have also been associated with higher tumor burden in multiple malignancies including leukemia, lymphoma, and multiple myeloma, which is likely to be associated with greater expansion of T cell populations and synchronous activation with BiTEs. Please refer to the Investigator's Brochure for additional information.**

Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the infusion with AMG 427 and at least **12** hours after the start of infusion, monitor subjects intensively for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, increase **in** transaminase**s, C-reactive protein [CRP], lactate dehydrogenase [LDH], ferritin, D-dimer, and erythrocyte sedimentation rate [ESR]**) which may be related to CRS. Cytokine release syndrome may be clinically associated with the development of fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, dyspnea**, and ICANS/neurotoxicity** as a consequence of systemic release of cellular cytokines such as TNF, **IL-1Ra,** IL-2, IL-3, IL-4, and IL-6 (**Morris et al, 2021;** Winkler et al, 1999). Potentially life-threatening complications of CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, and disseminated

intravascular coagulation (Lee et al, 2014) **and ICANS/neurotoxicity which may occur concurrently or immediately following CRS**.

Grading **of CRS should be performed according to the guidelines provided in Table 6** and management of CRS should be performed according to the guidelines provided in Table 7 (based on the adopted grading system referenced in Lee et al, 201**9**).

Table 6. Cytokine Release Syndrome Grading (ASTCT; Lee et al, 2019)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a single vasopressor (not including vasopressin)	Requiring multiple vasopressors (not including vasopressin)
		And/or[b]		
Hypoxia	None	Requiring low-flow (≤ 6 L/minute) nasal cannula or blow-by	Requiring high-flow nasal cannula (> 6 L/min), facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome

Organ toxicities associated with CRS may be graded according to CTCAE v4.0 but they do not influence CRS grading.

[a]Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

Table 7. Management of Cytokine Release Syndrome

Description of CRS Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 427
Fever (temperature ≥ 38°C) without hypotension and hypoxia	• Administer symptomatic treatment (eg, paracetamol/acetaminophen for fever). • **Administer tocilizumab[b] 4 to 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no clinical improvement in signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours (maximum of 3 doses in a 24-hour period; maximum total of 4 doses). If improving discontinue tocilizumab.** Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier. **If symptoms of grade 1 CRS do not improve after 24 hours consider managing as grade 2.**	

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Footnotes defined on next page of the table

Table 7. Management of Cytokine Release Syndrome

Description of CRS Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 427
Fever (temperature ≥ 38°C) with: • **Hypotension not requiring vasopressor AND/OR** • **Hypoxia requiring low-flow ≤ 6 L/min nasal cannula or blow-by**	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) • **Tocilizumab[b] 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no clinical improvement in signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours (maximum 3 doses in a 24-hour period; maximum total of 4 doses). If improving discontinue tocilizumab.** • **Dexamethasone 10 mg IV up to 3 times a day. Continue corticosteroids until the severity is grade 1 or less. If not improving manage as grade 3 below.** • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 100 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1 **for at least 24 hours prior to the next dose of AMG 427**. For subjects with extensive co-morbidities or poor performance status, manage per CRS guidance below.	If hypotension worsens or persists 2 hours after adequate medical management, interrupt AMG 427 until CRS is **g**rade ≤ 1 **for at least 24 hours prior to the next dose of AMG 427**. Refer to re-start criteria below **for CRS grade 3**. If symptoms progress to grade 3 criteria, see row below. Permanently discontinue AMG 427 if there is no improvement to CRS ≤ grade 1 within 7 days.

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Footnotes defined on next page of the table

Table 7. Management of Cytokine Release Syndrome

Description of CRS Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 427
Fever (temperature ≥ 38°C) with: • **Hypotension requiring a single vasopressor (not including vasopressin) AND/OR** • **Hypoxia requiring high-flow (> 6 L/min) nasal cannula, facemask, nonrebreather mask, or Venturi mask**	Admit to intensive care unit **(ICU)** for close clinical and vital sign monitoring per institutional guidelines. • **Tocilizumab[b] 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no clinical improvement in signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours (maximum 3 doses in a 24-hour period). If improving discontinue tocilizumab.** Administer dexamethasone **10-20 mg up to three times a day. If improving manage as appropriate grade above and continue corticosteroids until severity is grade 1 or less, then taper as clinically appropriate.** **Consider methylprednisolone up to 1000 mg or as per institutional practice.**	**Subjects who experience CRS grade 3 should have next dose delayed until CRS resolves to grade ≤ 1 for at least 24 hours prior to the next dose of AMG 427 (including isolated lab abnormalities and organ toxicity labs, except for LFTs, which must resolve to grade 2 or less), and should have next dose(s) reduced by one-half or more, if given on scheduled day (please consult with the study medical monitor).** Permanently discontinue AMG 427 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. Permanently discontinue AMG 427 if CRS grade 3 occurs at the initial run in dose (ie, at MTD1).

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Footnotes defined on next page of the table

Table 7. Management of Cytokine Release Syndrome

Description of CRS Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 427
• **Fever (temperature ≥ 38°C) with:** • **Hypotension requiring multiple vasopressors (excluding vasopressin) AND/OR** • **Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)**	Admit to **ICU** for close clinical and vital sign monitoring per institutional guidelines. • **Tocilizumab[b] 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no clinical improvement in signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours (maximum 3 doses in a 24-hour period). If improving discontinue tocilizumab.** **Administer methylprednisolone up to 1000 mg once per day for 3 days. If improving manage as appropriate grade above and continue corticosteroids until severity is grade 1 or less then taper as clinically appropriate.** **If not improving consider methyl prednisolone 1000 mg two to three times a day or alternate therapy.**	Immediately stop the infusion and permanently discontinue AMG 427 therapy.

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BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = Cytokine Release Syndrome; **ICU = intensive care unit; IL-6 = interleukin 6; IL-6R = interleukin 6 receptor;** IV = Intravenous; **LFT(s) = liver function test(s);** MTD = maximum-tolerated dose

[a] **G**rading system for CRS (Lee et al, 201**9**)

[b] **If tocilizumab is not available, another IL-6/IL-6R inhibitor eg, siltuximab may be used per institutional practice for CRS.**

Re-start of treatment after CRS:

Please refer to the general guidance for re-start of treatment after adverse events in Section 6.2.1.4

For grade 3 and 4 CRS, please see Section 6.2.1.3 for DLT considerations.

Immune-effector Cell-associated Neurotoxicity Syndrome (ICANS):

Immune-effector cell-associated neurotoxicity syndrome (ICANS) typically manifests as a toxic encephalopathy and starts with word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills, and somnolence. In more severe cases, seizures, motor weakness, cerebral edema and coma have been noted. The majority of patients who develop clinical features of ICANS will have had preceding CRS. Cytokine release syndrome can, therefore, be considered an 'initiating event' or cofactor for ICANS. Neurotoxicity generally occurs after the symptoms of CRS have subsided, although, less frequently, concurrent presentation of CRS and ICANS can occur. Similar to CRS, ICANS is reversible in most patients with no permanent neurological deficits (Schuster et al, 2019; Neelapu et al, 2018; Santomasso et al, 2018; Gust et al, 2017).

For this trial, ICANS will be managed using the criteria referenced in the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Criteria for ICANS associated with immune effector cells (Lee et al, 2019). While the grading system has been developed in large part from CAR-T therapies, symptoms of ICANS may be shared among immune effector-cell associated therapies such as BiTE® molecules. Although there may be a wide range of symptoms associated with ICANS, subjects may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

ICANS grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause. Refer to the immune effector cell-associated encephalopathy (ICE) score below for grading of ICANS.

<u>ICE Assessment Tool</u>

- **Orientation: Orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**

- Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- Attention: ability to count backwards from 100 by 10: 1 point

ICE scoring

- 7-9, grade 1
- 3-6, grade 2
- 0-2, grade 3
- 0 due to subject unarousable and unable to perform ICE assessment, grade 4

Table 8. ASTCT Immune Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (subject is unarousable and unable and unable to perform ICE)
Depression level of consiousness[c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune-effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable.

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v4.0.

Source: Lee et al, 2019

Assessment and Supportive Care Recommendations (all grades)

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- Magnetic resonance imaging (MRI) of the brain with and without contrast (or brain computed tomography [CT] if MRI is not feasible) for ≥ grade 2 neurotoxicity
- Neurology consultation at first sign of neurotoxicity
- Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity
- Aspiration precautions; IV hydration
- Use caution when prescribing medications that can cause CNS depression (aside from those needed for seizure prophylaxis/treatment)

Table 9. Assessment and Supporting Care Recommendations

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
Grade 1	• Supportive care • If neurotoxicity is observed within 6 hours of dosing, consider anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per institutional practice).	In the setting of grade ≥ 3 CRS with hypotension, tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose) If neurotoxicity is observed within 6 hours of dosing, consider anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per institutional practice).
Grade 2[c]	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen. • Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per institutional	Anti-IL-6 therapy as per grade 1 Consider transferring subject to ICU if neurotoxicity associated with grade ≥ 2 CRS Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
	practice) if neurotoxicity is observed within 6 hours of dosing.	institutional practice) if neurotoxicity is observed within 6 hours of dosing.
Grade 3[c]	• Supportive care • Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[a] • Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days if neurotoxicity is observed within 6 hours of dosing. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject had persistent grade ≥ 3 neurotoxicity.	Anti-IL-6 therapy as per grade 1 Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days if neurotoxicity is observed within 6 hours of dosing
Grade 4[c]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[a,b] • Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per institutional practice) if neurotoxicity is observed within 6 hours of dosing • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject has persistent grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per grade 1 Consider Anakinra 100 mg subcutaneously every 12 hours for up to 7 days (or another IL-1 receptor inhibitor per institutional practice) if neurotoxicity is observed within 6 hours of dosing.

CRS = cytokine release syndrome; CT = computed tomography; ICU = intensive care unit; IL-1 = interleukin 1; IL-6 = interleukin 6; IV = intravenous; MRI = magnetic resonance imaging.
[a] Antifungal prophylaxis should be strongly considered in subjects receiving steroids for the treatment of CRS and/or neurotoxicity.
[b] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
[c] Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.
[d] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses

Tumor Lysis Syndrome

Subjects with AML and WBC < 10 000/mcL (or 10 cells x 10^9/L) are considered to be at low risk for tumor lysis syndrome. White blood cells (WBC) > 10 000/mcL and < 50 000/mcL are considered to be at intermediate risk, and subjects with WBC > 50 000/mcL are considered at high risk. This protocol requires that subjects have a maximum WBC count of 15 000/mcL or 15 cells x 10^9/L.

Additional high risk features include baseline uric acid > 450 μmol/L (7.5 mg/dL), serum creatinine > 1.4 mg/dL, and lactate dehydrogenase (LDH) greater than the ULN.

Subjects with intermediate risk WBC count and elevated baseline uric acid (> 450 μmol /L), serum creatinine > 1.4 mg/dL, or LDH greater than ULN will be recommended to receive allopurinol prophylaxis. Typical dosing is 600 - 800 mg/day administered twice a day (BID) or 3 times a day (TID) and should begin 3 days before the first dose of study drug. Subjects should be well hydrated and supplemented with intravenous fluid as clinically indicated.

For grade 3 and 4 TLS, please see Section 6.2.1.3 for DLT considerations.

Infection Prophylaxis

Subjects who may experience neutropenia for 7 days or longer are at a high risk for infectious complications. As appropriate, these subjects should be administered prophylactic antibacterial (eg, fluoroquinolones), antifungal, and antiviral medications. These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification.

6.7 Medical Devices

Depending on the dose, the investigational product must be administered using syringe pumps (for IV lower doses) or infusion pumps (for higher IV doses) approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment. Investigational product infusion for solution will be prepared in syringes or bags for IV infusion and delivered through infusion lines.

Other non-investigational medical devices **may be used in the conduct of this stuady as part of standard of care.**

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not **usually** provided or reimbursed by Amgen (except, **for example,** if required by local regulation). The investigator will be responsible for obtaining supplies **of** these **devices**.

6.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or by **(2)** distributors and partners for

whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

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

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided.

6.9 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

Any anti-tumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, immunotherapy or any biological response modifiers, any other investigational agent, chronic systemic corticosteroid therapy, other immunosuppressive therapies, or stem-cell transplantation is not allowed.
Exception: Hydroxyurea is allowed to control WBCs as described in Section 6.3.

Radiotherapy is not permitted except for palliation of symptoms and should be discussed with the Amgen medical monitor first. Investigators should ensure that the need for radiation does not indicate progressive disease and that for subjects with measurable disease, radiation is not to the sole site of measurable disease.

Live vaccines are prohibited during treatment with AMG 427.

The following procedures should also not be undertaken within the time frames specified prior to enrollment and during the study:

- Participation in an investigational study (drug or device) within 14 days of study day 1
- Major surgery within 28 days of study day 1 (with the exception of biopsy or insertion of central venous catheter)
- Enrollment into another investigational drug or device study

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Summary of Schedule of Assessments:

Schedule	Dosing Schedule	Cycle/Assessment	Table Number
Schedule A **(CLOSED)**	Days 1 and 5	Cycle 1	Table 10
		Cycle 2	Table 11

		Cycle ≥ 3	Table 12
	Days 1, 5, 12, and 19	Cycle 1	Table 13
		Cycle 2	Table 14
		Cycle ≥ 3	Table 15
Schedule B **(CLOSED)**	Etanercept substudy		Section 7.1.1
Schedule C	Days 1, 3, 5, and 8	Cycle 1	Table 16
		Cycle 2	Table 17
		Cycle ≥ 3	Table 18
		MRD+ Group Only Whole Blood MRD collection	Table 22
	Days 1, 3, 5, 8, 12, and 19	Cycle 1	Table 19
		Cycle 2	Table 20
		Cycle ≥ 3	Table 21
		MRD+ Group Only Whole Blood MRD collection	Table 23

Table 10. Schedule of Assessments: Schedule A Cycle 1 (Days 1 and 5)

	SCR	Treatment Cycle 1																												
Week		1																											2	
Cycle Day	-14 to -1	1										2	3	4	5[a]													6	7	8	14
Hours		Pre-dose	Relative to start of infusion												Pre-dose	Relative to start of infusion															
			0	1[b]	2	3	4	6	8	12	16	20	24	48	72		0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS																														
Informed consent	X																													
Hospitalization[c]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Demog / Med and Surg hist / Height	X																													
Concomitant Medications	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Serious adverse events review	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Adverse events	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Physical Exam	X	X											X	X	X	X											X	X	X	
ECOG	X	X																												
Weight	X	X																												
Vital signs, pulse oximetry[d]	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X[f]	X		X[b]												X		X[b]												
LABORATORY ASSESSMENTS																														
Serum pregnancy test[g]	X																													
Coagulation	X	X							X				X	X	X	X											X	X	X	
Hematology, Chemistry	X	X							X				X	X	X	X											X	X	X	X
Urinalysis	X	X														X													X	
Hepatitis serology	X																													
eGFR[h]	X																													
[redacted]																														
INVESTIGATIONAL PRODUCT DOSING																														
AMG 427 short term IV Infusion			X														X													
Premedication[i]		X														X														
BIOMARKER ASSESSMENTS																														
[redacted]																														
PK ASSESSMENTS																														
AMG 427 PK[k]		X		X[b]				X					X	X		X		X[b]				X		X			X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS																														
[redacted]																														

Footnotes defined on next page

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; IV = intravenous; PK = pharmacokinetic; SCR = Screening; [redacted]

[a] The Dose Level Review Team may recommend to change timing of D5 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[b] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~90 minutes).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject's discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Schedule for triplicate ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

[f] Two (2) sets of triplicate ECGs collected at Screening.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[h] The estimated glomerular filtration rate (eGFR) will be calculated based on institutional standards.

[i] Premedication should be administered 1 hour before the start of infusion and prior to each step-up dose of AMG 427 infusion to mitigate the risk for the prevention of CRS.

[redacted]

[k] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

Table 11. Schedule of Assessments: Schedule A Cycle 2 (Days 1 and 5)

	Treatment Cycle 2																										
Week	1																									2	
Cycle Day	1										2	3	4	5[a]									6	7	8	14	
Hours	Pre-dose	Relative to start of infusion												Pre-dose	Relative to start of infusion												
		0	1[b]	2	3	4	6	8	12	16	20	24	48	72		0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS																													
Hospitalization[c]	→																												
Concomitant Medications	→																												
Serious adverse events review	→																												
Adverse events	→																												
Physical Exam	X											X	X	X	X											X	X	X	
ECOG	X																												
Weight	X																												
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X[b]												X		X[b]												
LABORATORY ASSESSMENTS																													
Coagulation	X							X				X	X	X	X											X	X	X	
Hematology, Chemistry	X							X				X	X	X	X											X	X	X	X
Urinalysis	X														X														
[redacted]																													
INVESTIGATIONAL PRODUCT DOSING																													
AMG 427 short term IV Infusion		X														X													
Premedication[e]	X														X														
BIOMARKER ASSESSMENTS																													
[redacted]																													
PK ASSESSMENTS																													
AMG 427 PK[f]	X		X[b]				X					X	X		X		X[b]				X		X			X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS																													
[redacted]																													

Footnotes defined on next page

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PK = pharmacokinetic; [redacted]

[a] The Dose Level Review Team may recommend to change timing of D5 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[b] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~90 minutes).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Premedication should be administered 1 hour before the start of infusion and prior to each step-up dose of AMG 427 infusion to mitigate the risk for the prevention of CRS.

[f] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

Table 12. Schedule of Assessments: Schedule A Cycle 3 and Beyond (Days 1 and 5)

	Treatment Cycle 3 and following																								SFU[a]	LTFU[b]
Week	1																						2		EOT	4 weeks post last dose of AMG 427 (+1 week)	Up to 2 yrs after 1st dose of AMG 427; every 8 weeks (±2 weeks)
Cycle Day	1										5[c]												8	14			
Hours	Pre-dose	Relative to start of infusion									Pre-dose	Relative to start of infusion											72				
		0	1[d]	2	3	4	6	8	12	16	20		0	1[d]	2	3	4	6	8	12	16	20					
GENERAL AND SAFETY ASSESSMENTS																											
Hospitalization[e]																											
Concomitant Medications	→											→															X[f]
Serious adverse events review	→											→															→
Adverse events	→											→															
Physical Exam	X											X													X	X	
ECOG	X																									X	
Weight	X																									X	
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	X	
ECG triplicate measurement																									X	X	
LABORATORY ASSESSMENTS																											
Coagulation	X											X											X		X	X	
Hematology, Chemistry	X											X											X	X	X	X	
Urinalysis	X											X													X		
Urine Pregnancy Test																										X[o]	
[redacted]																											
INVESTIGATIONAL PRODUCT DOSING																											
AMG 427 short term IV Infusion		X											X														
Premedication[i]	X											X															
BIOMARKER ASSESSMENTS																											
[redacted]																											
PK ASSESSMENTS																											
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]									X		X	X	
DISEASE & BIOMARKER ASSESSMENTS																											
[redacted]																											

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; IV = intravenous; LTFU = long term follow-up; PK = pharmacokinetic; SFU = safety follow-up

[a] The safety follow-up (SFU) visit occurs 4 weeks (+1 week) after the last infusion of AMG 427. For subjects enrolled in the escalation phase, this visit may also be the end of study (EOS) visit.

[b] The long term follow-up (LTFU) period may consist of a telephone call performed every 8 weeks (± 2 weeks) after the SFU visit, to assess survival, disease status and anti-AML therapy(ies). LTFU applies only to subjects enrolled in the dose expansion phase. The last contact with a subject may also signify EOS. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen.**

[c] The Dose Level Review Team may recommend to change timing of D5 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[d] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~90 minutes).

[e] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[f] Collect anti-AML treatments only.

[g] Vital signs/pulse oximetry will also be assessed prior when the subject leaves the clinic in order to detect possible signs and symptoms of infusion reactions.

[h] Time points for vital sign and pulse oximetry measurements after the end of infusion time point apply only if the subject is still at the clinic at the time.

[i] Premedication should be administered 1 hour before the start of infusion and prior to each step-up dose of AMG 427 infusion to mitigate the risk for the prevention of CRS.

[j] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[k] Beginning with cycle 4, only predose PK samples are collected (predose: D1, D5), EOT, and SFU for cycles 4 through 12. Day 8 PK collection will not be collected C4 and beyond.

[redacted]

[o] If applicable, urine pregnancy test required 4 weeks after the last dose of AMG 427.

Table 13. Schedule of Assessments: Schedule A Cycle 1 (Days 1, 5, 12 and 19)

	SCR	Treatment Cycle 1													
Week		1													
Cycle Day	-14 to -1	1											2	3	4
Hours			Relative to start of infusion												
		Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	48	72
ENERAL AND SAFETY ASSESSMENTS															
Informed consent	X														
Hospitalization[c]		→													
Demog / Med and Surg hist / Height	X														
Concomitant Medications	X	→													
Serious adverse events review	X	→													
Adverse events	X	→													
Physical Exam	X	X											X	X	X
ECOG	X	X													
Weight	X	X													
Vital signs, pulse oximetry[d]	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X[f]	X		X[b]											
LABORATORY ASSESSMENTS															
Serum pregnancy test[g]	X														
Coagulation	X	X							X				X	X	X
Hematology, Chemistry	X	X							X				X	X	X
Urinalysis	X	X													
Hepatitis serology	X														
eGFR[h]	X														
[redacted]															
IVESTIGATIONAL PRODUCT DOSING															
AMG 427 short term IV Infusion			X												
Premedication[i]		X													
BIOMARKER ASSESSMENTS															
[redacted]															
PK ASSESSMENTS															
AMG 427 PK[k]		X		X[b]				X					X	X	
DISEASE & BIOMARKER ASSESSMENTS															
[redacted]															

Week	1													2
Cycle Day	5[a]											6	7	8
Hours		Relative to start of infusion												
	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	48	72
ENERAL AND SAFETY ASSESSMENTS														
Informed consent														
Hospitalization[c]	→													
Demog / Med and Surg hist / Height														
Concomitant Medications	→													
Serious adverse events review	→													
Adverse events	→													
Physical Exam	X											X	X	X
ECOG														
Weight														
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X		X[b]											
LABORATORY ASSESSMENTS														
Serum pregnancy test[g]														
Coagulation	X											X	X	X
Hematology, Chemistry	X											X	X	X
Urinalysis	X													
Hepatitis serology														
eGFR[h]														
IVESTIGATIONAL PRODUCT DOSING														
AMG 427 short term IV Infusion		X												
Premedication[i]	X													
BIOMARKER ASSESSMENTS														
PK ASSESSMENTS														
AMG 427 PK[k]	X		X[b]											
DISEASE & BIOMARKER ASSESSMENTS														

Week	2													3
Cycle Day	12[a]											13	14	15
Hours		Relative to start of infusion												
	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	48	72
ENERAL AND SAFETY ASSESSMENTS														
Informed consent														
Hospitalization[c]	→													
Demog / Med and Surg hist / Height														
Concomitant Medications	→													
Serious adverse events review	→													
Adverse events	→													
Physical Exam	X											X	X	X
ECOG														
Weight														
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X		X[b]											
LABORATORY ASSESSMENTS														
Serum pregnancy test[g]														
Coagulation	X											X	X	X
Hematology, Chemistry	X											X	X	X
Urinalysis	X													
Hepatitis serology														
eGFR[h]														
IVESTIGATIONAL PRODUCT DOSING														
AMG 427 short term IV Infusion		X												
Premedication[i]	X													
BIOMARKER ASSESSMENTS														
PK ASSESSMENTS														
AMG 427 PK[k]	X		X[b]									X		
DISEASE & BIOMARKER ASSESSMENTS														

Week	3													4	
Cycle Day	19[a]											20	21	22	28
Hours		Relative to start of infusion													
	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
ENERAL AND SAFETY ASSESSMENTS															
Informed consent															
Hospitalization[c]	→														
Demog / Med and Surg hist / Height															
Concomitant Medications	→														
Serious adverse events review	→														
Adverse events	→														
Physical Exam	X											X	X	X	X
ECOG															
Weight															
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X		X[b]												
LABORATORY ASSESSMENTS															
Serum pregnancy test[g]															
Coagulation	X											X	X	X	
Hematology, Chemistry	X											X	X	X	X
Urinalysis	X													X	
Hepatitis serology															
eGFR[h]															
IVESTIGATIONAL PRODUCT DOSING															
AMG 427 short term IV Infusion		X													
Premedication[i]	X														
BIOMARKER ASSESSMENTS															
PK ASSESSMENTS															
AMG 427 PK[k]	X		X[b]				X					X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS															

Footnotes defined on next page

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; IV = intravenous; PK = pharmacokinetic; SCR = Screening; [redacted]

[a] The Dose Level Review Team may recommend to change timing of dose within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[b] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~90 minutes).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Schedule for triplicate ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

[f] Two (2) sets of triplicate ECGs collected at Screening.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[h] The estimated glomerular filtration rate (eGFR) will be calculated based on institutional standards.

[redacted]

[j] Whole blood for peripheral blood mononuclear cells (PBMCs) collected prior to the infusion on cycle 1 day 1 only if subject provides consent for collection of the pharmacogenetic (PG) sample.

[k] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

Table 14. Schedule of Assessments: Schedule A Cycle 2 (Days 1, 5, 12 and 19)

	Treatment Cycle 2																																																			
Week	1																												2												3												4
Cycle Day	1											2	3	4	5[a]											6	7	8	12[a]											14	19[a]											21	28
Hours	Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion													Pre-dose	Relative to start of infusion											Pre-dose	Relative to start of infusion											
		0	1[b]	2	3	4	6	8	12	16	20	24	48	72		0	1[b]	2	3	4	6	8	12	16	20	24	48	72		0	1[b]	2	3	4	6	8	12	16	20	48		0	1[b]	2	3	4	6	8	12	16	20	48	
GENERAL AND SAFETY ASSESSMENTS																																																					
Hospitalization[c]	→ (through Day 8)																																																				
Concomitant Medications	→																																																				
Serious adverse events review	→																																																				
Adverse events	→																																																				
Physical Exam	X											X	X	X	X											X	X	X	X											X	X											X	X
ECOG	X																																																				
Weight	X																																																				
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X		X[b]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X		X[b]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X
ECG triplicate measurement	X		X[b]												X		X[b]												X		X[b]										X		X[b]										
LABORATORY ASSESSMENTS																																																					
Coagulation	X							X				X	X	X	X											X	X	X	X											X	X											X	
Hematology, Chemistry	X							X				X	X	X	X											X	X	X	X											X	X											X	X
Urinalysis	X														X														X												X												
[redacted]																																																					
INVESTIGATIONAL PRODUCT DOSING																																																					
AMG 427 short term IV Infusion		X														X														X												X											
Premedication[f]	X														X														X												X												
BIOMARKER ASSESSMENTS																																																					
[redacted]																																																					
PK ASSESSMENTS																																																					
AMG 427 PK[g]	X		X[b]				X					X	X		X		X[b]				X		X			X	X	X	X		X[b]				X						X		X[b]			X	X					X	X
DISEASE & BIOMARKER ASSESSMENTS																																																					
[redacted]																																																					

Footnotes defined on next page

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PK = pharmacokinetic; [redacted]

[a] The Dose Level Review Team may recommend to change timing of dose within a window of ±1-3 days. In this case, timing of the following visits would be adjusted accordingly

[b] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~ 90 minutes).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).
[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital or leaves the clinic in order to detect possible signs and symptoms of infusion reactions.
[e] Time points for vital sign and pulse oximetry measurements after the end of infusion time point apply only if the subject is still at the clinic at the time.
[f] Premedication should be administered 1 hour before the start of infusion and prior to each step-up dose of AMG 427 infusion to mitigate the risk for the prevention of CRS.
[g] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

Table 15. Schedule of Assessments: Schedule A Cycle 3 and beyond (Days 1, 5, 12, and 19)

	Treatment Cycle 3 and following																																		EOT	SFU[a]	LTFU[b]
Week	1											2												3											4			
Cycle Day	1											5[c]												12[c]											19[c]											28			
Hours	Pre-dose	Relative to start of infusion										Pre-dose	Relative to start of infusion											Pre-dose	Relative to start of infusion										Pre-dose	Relative to start of infusion												
		0	1[d]	2	3	4	6	8	12	16	20		0	1[d]	2	3	4	6	8	12	16	20		0	1[d]	2	3	4	6	8	12	16	20		0	1[d]	2	3	4	6	8	12	16	20			
GENERAL AND SAFETY ASSESSMENTS																																																	
Hospitalization[e]																																																
Concomitant Medications	→											→												→											→											X[f]	
Serious adverse events review	→											→												→											→												
Adverse events	→											→												→											→												
Physical Exam	X											X												X												X	X	
ECOG	X																																			X	X	
Weight	X																																					
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]		X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]		X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]		X	X	X
ECG triplicate measurement																																				X	X	
LABORATORY ASSESSMENTS																																						
Coagulation	X											X												X												X	X	
Hematology, Chemistry	X											X												X											X	X	X	
Urinalysis	X											X												X												X		
Urine Pregnancy Test																																					X[c]	
INVESTIGATIONAL PRODUCT DOSING																																						
AMG 427 short term IV infusion		X											X												X														
Premedication[i]	X											X												X														
BIOMARKER ASSESSMENTS																																						
PK ASSESSMENTS																																						
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]										X[k]	X[d]										X[k]		X[d]									X	X	X	
DISEASE & BIOMARKER ASSESSMENTS																																						

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; IV = intravenous; LTFU = long term follow-up; PK = pharmacokinetic; SFU = safety follow-up

[a] The safety follow-up (SFU) visit occurs 4 weeks (+1 week) after the last infusion of AMG 427. For subjects enrolled in the escalation phase, this visit may also be the end of study (EOS) visit.

[b] The long term follow-up (LTFU) period may consist of a telephone call performed every 8 weeks (± 2 weeks) after the SFU visit to assess survival, disease status, and anti-AML therapy(ies). LTFU applies only to subjects enrolled in the dose expansion phase. The last contact with a subject may also signify EOS. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen.**

[c] The Dose Level Review Team may recommend to change timing of dose within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[d] Collect assessments at the end of infusion (EOI). End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, ~90 minutes).

[e] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of infusion for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[f] Collect anti-AML treatments only.

[g] Vital signs/pulse oximetry will also be assessed prior when the subject leaves the clinic in order to detect possible signs and symptoms of infusion reactions.

[h] Time points for vital sign and pulse oximetry measurements after the end of infusion time point apply only if the subject is still at the clinic at the time.

[i] Premedication should be administered 1 hour before the start of infusion and prior to each step-up dose of AMG 427 infusion to mitigate the risk for the prevention of CRS.

[j] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[k] Beginning with cycle 4, ONLY predose PK samples are collected (Predose: D1, D5, D12, D19), EOT and SFU for cycles 4 through 12. Day 28 PK collection will not be collected C4 and beyond.

[redacted]

[o] If applicable, urine pregnancy test required 4 weeks after the last dose of AMG 427.

7.1.1 Schedule of Assessments: Schedule B (etanercept substudy – CLOSED)

- Only for the etanercept (Enbrel) substudy ([redacted]):
- Schedule A + etanercept to be administered subcutaneously (50 mg SC) on day - 2 (minus 2) prior to each cycle

  All other study measures and schedules remain unchanged. Please refer to Schedule A (Table 10 - Table 15) for daily visits and sample collections for etanercept subjects.
- Schedule C may also be considered with sponsor approval (Table 16 - Table 21).
  - The MRD+ Group will use Schedule C for all cycle collections and Table 22 or Table 23 for addition**al** whole blood MRD collections**, as applicable**.

Table 16. Schedule of Assessments: Schedule C Cycle 1 (Days 1, 3, 5, and 8)

	SCR	Treatment Cycle 1																																																		
Week		1																																				2														
Cycle Day	-14 to -1	1											2	3[a]											4	5[a]											6	8[a]											9	10	11	14
			Relative to start of dose												Relative to start of dose												Relative to start of dose												Relative to start of dose													
Hours		Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	Pre-dose	0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS																																																				
Informed consent	X																																																			
Hospitalization[c]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Demog / Med and Surg hist / Height	X																																																			
Concomitant Medications	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious adverse events review	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse events	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Physical Exam	X	X											X	X											X	X											X	X											X	X	X	
ECOG	X	X																																																		
Weight	X	X																																																		
Vital signs, pulse oximetry[d]	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement[e]	X[f]	X		X[b]										X		X[b]										X		X[b]										X		X[b]												
LABORATORY ASSESSMENTS																																																				
Serum pregnancy test[g]	X																																																			
Coagulation	X	X							X				X	X											X	X											X	X											X	X	X	
Hematology, Chemistry	X	X							X				X	X											X	X											X	X											X	X	X	X
Urinalysis	X	X												X												X												X													X	
Hepatitis serology	X																																																			
eGFR[h]	X																																																			
[redacted]																																																			
INVESTIGATIONAL PRODUCT DOSING																																																				
AMG 427 dose[o]			X												X												X												X													
Premedication[i]		X												X												X												X														
BIOMARKER ASSESSMENTS																																																				
[redacted]																																																			
PK ASSESSMENTS																																																				
AMG 427 PK[k]		X		X[b]				X					X	X		X[b]				X					X	X		X[b]				X		X			X	X		X[b]				X		X			X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS																																																			
[redacted]																																																			

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; eIV = extended IV; IV = intravenous; PK = pharmacokinetic; SCR = Screening

[a] The Dose Level Review Team may recommend to change timing of D3, D5, D8 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[b] Collect assessments at the end of infusion (EOI). For the First-in-Human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~ 90 minutes, eIV~ 24 hours).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Schedule for triplicate ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

[f] Two (2) sets of triplicate ECGs collected at Screening.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[h] The estimated glomerular filtration rate (eGFR) will be calculated based on institutional standards
[i] Premedication should be administered within 1 hour before the start of AMG 427 dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.

[redacted]

Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

[o] Of note, for the eIV cohorts, please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] μg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] μg over 24 hours), day 5 and day 8 will be short term IV infusions (~ 90 minutes each).

Table 17. Schedule of Assessments: Schedule C Cycle 2 (Days 1, 3, 5, and 8)

	Treatment Cycle 2																																																		
Week	1																																			2														
Cycle Day	1											2	3[a]											4	5[a]											6	8[a]											9	10	11	14
Hours	Pre-dose	Relative to start of dose											Pre-dose	Relative to start of dose											Pre-dose	Relative to start of dose											Pre-dose	Relative to start of dose													
		0	1[b]	2	3	4	6	8	12	16	20	24		0	1[b]	2	3	4	6	8	12	16	20	24		0	1[b]	2	3	4	6	8	12	16	20	24		0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS																																																			
Hospitalization[c]	→																																																		
Concomitant Medications	→																																																		
Serious adverse events review	→																																																		
Adverse events	→																																																		
Physical Exam	X											X	X											X	X											X	X											X	X	X	
ECOG	X																																																		
Weight	X																																																		
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X[b]										X		X[b]										X		X[b]										X		X[b]												
LABORATORY ASSESSMENTS																																																			
Coagulation	X							X				X	X											X	X											X	X											X	X	X	
Hematology, Chemistry	X							X				X	X											X	X											X	X											X	X	X	X
Urinalysis	X												X												X												X														
[redacted]																																																			
INVESTIGATIONAL PRODUCT DOSING																																																			
AMG 427 dose[i]		X												X												X												X													
Premedication[e]	X												X												X												X														
BIOMARKER ASSESSMENTS																																																			
[redacted]																																																			
PK ASSESSMENTS																																																			
AMG 427 PK[f]	X		X[b]				X					X	X		X[b]				X					X	X		X[b]				X		X			X	X		X[b]				X		X			X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS																																																			
[redacted]																																																			

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eIV = extended IV; IV = intravenous; PK = pharmacokinetic

[a] The Dose Level Review Team may recommend to change timing of D3, D5, D8 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly

[b] Collect assessments at the end of infusion (EOI). For the First-in-human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~90 minutes, eIV ~24 hours).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Premedication should be administered within 1 hour before the start of AMG 427 dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.

[f] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

[i] Of note, for the eIV cohorts, please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] μg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] μg over 24 hours), day 5 and day 8 will be short term IV infusions (~ 0 minutes each).

Table 18. Schedule of Assessments: Schedule C Cycle ≥ 3 (Days 1, 3, 5, and 8)

	Treatment Cycle 3 and following																					
Week	1																					
Cycle Day	1											3[c]										
Hours	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20
GENERAL AND SAFETY ASSESSMENTS																						
Hospitalization[e]																						
Concomitant Medications	→																					
Serious adverse events review	→																					
Adverse events	→																					
Physical Exam	X											X										
ECOG	X																					
Weight	X																					
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
ECG triplicate measurement																						
LABORATORY ASSESSMENTS																						
Coagulation	X											X										
Hematology, Chemistry	X											X										
Urinalysis	X											X										
Urine Pregnancy Test																						
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 427 Dose[q]		X											X									
Premedication[i]	X											X										
BIOMARKER ASSESSMENTS																						
[redacted]																						
PK ASSESSMENTS																						
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]								
DISEASE & BIOMARKER ASSESSMENTS																						
[redacted]																						

	Treatment Cycle 3 and following																								EOT	SFU[a]	LTFU[b]
Week	1											2														4 weeks post last dose of AMG 427 (+1 week)	Up to 2 yrs after 1st dose of AMG 427; every 8 weeks (±2 weeks)
Cycle Day	5[c]											8[a]											11	14			
Hours	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	72				
GENERAL AND SAFETY ASSESSMENTS																											
Hospitalization[e]																											
Concomitant Medications	→																									→	X[f]
Serious adverse events review	→																										→
Adverse events	→																									→	
Physical Exam	X											X													X	X	
ECOG																										X	
Weight																										X	
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	X	
ECG triplicate measurement																									X	X	
LABORATORY ASSESSMENTS																											
Coagulation	X											X											X		X	X	
Hematology, Chemistry	X											X											X	X	X	X	
Urinalysis	X											X													X		
Urine Pregnancy Test																										X[o]	
[redacted]																											
INVESTIGATIONAL PRODUCT DOSING																											
AMG 427 Dose[q]		X											X														
Premedication[i]	X											X															
BIOMARKER ASSESSMENTS																											
[redacted]																											
PK ASSESSMENTS																											
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]											X	X	
DISEASE & BIOMARKER ASSESSMENTS																											
[redacted]																											

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; eIV = extended IV; IV = intravenous; LTFU = long term follow-up; PK = pharmacokinetic; SFU = safety follow-up

[a] The safety follow-up (SFU) visit occurs 4 weeks (+1 week) after the last dose of AMG 427. For subjects enrolled in the escalation phase, this visit may also be the end of study (EOS) visit.

[b] The long term follow-up (LTFU) period may consist of a telephone call performed every 8 weeks (± 2 weeks) to assess disease status and anti-AML therapy(ies). LTFU applies only to subjects enrolled in the dose expansion phase. The last contact with a subject may also signify EOS. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen.**

[c] The Dose Level Review Team may recommend to change timing of D3, D5, D8 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[d] Collect assessments at the end of infusion (EOI). For the First-in-Human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~90 minutes, eIV~ 24 hours).

[e] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).
[f] Collect anti-AML treatments only.
[g] Vital signs/pulse oximetry will also be assessed prior when the subject leaves the clinic in order to detect possible signs and symptoms of infusion reactions.
[h] Time points for vital sign and pulse oximetry measurements after the end of dose time point apply only if the subject is still at the clinic at the time.
[i] Premedication should be administered within 1 hour before the start of dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.
[j] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.
[k] For cycles 4 through 12, only predose PK samples are collected (Predose: D1, D3, D5, D8), EOT and SFU for cycles 4 through 12. Day 8 PK collection will not collected C4 and beyond.

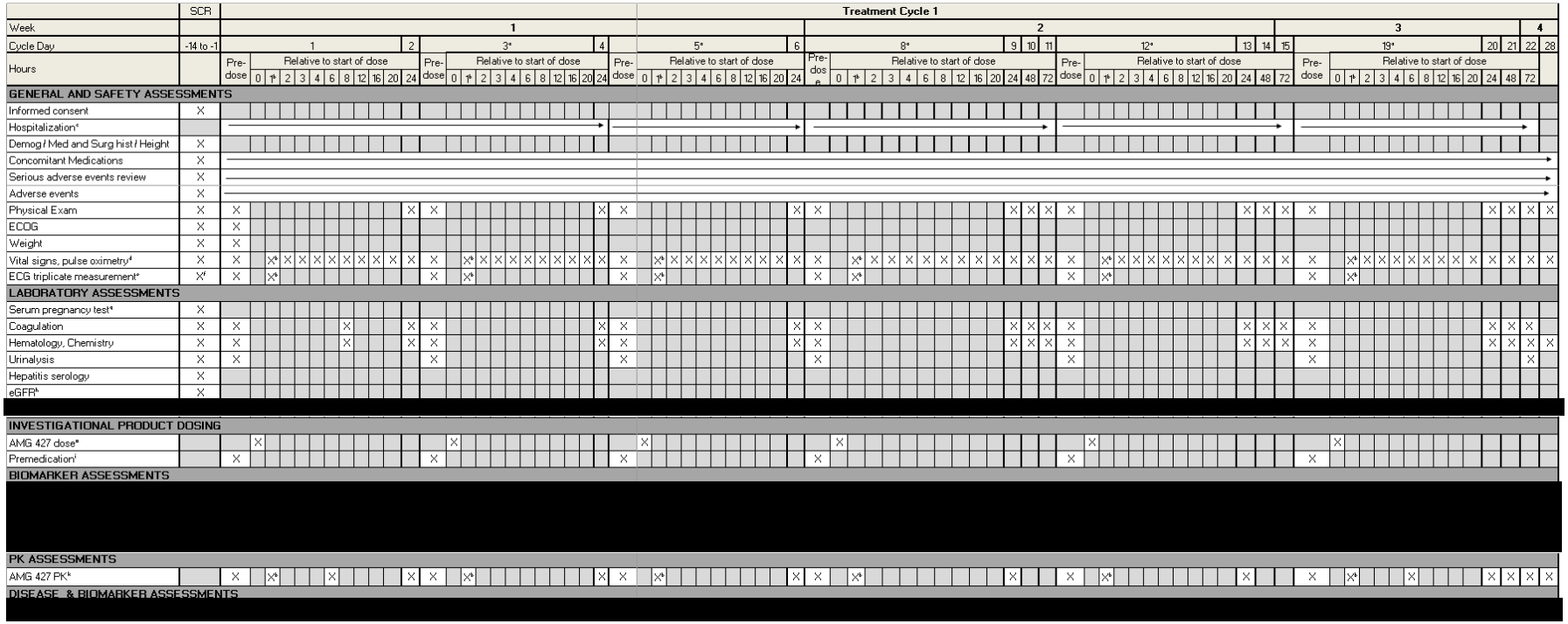
[redacted]

[o] If applicable, urine pregnancy test required 4 weeks after the last dose of AMG 427.

[redacted]

[q] Of note, for the eIV cohorts, please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] µg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] µg over 24 hours), day 5 and day 8 will be short term IV infusions (~90 minutes each).

Table 19. Schedule of Assessments: Schedule C- Cycle 1 (Days 1, 3, 5, 8, 12, and 19)



ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; eIV = extended IV; IV = intravenous; PK = pharmacokinetic; SCR = Screening

[a] The Dose Level Review Team may recommend to change timing of D3/D5/D8//D12/D19 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[b] Collect assessments at the end of infusion (EOI). For the First-in-Human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~90 minutes, eIV~ 24 hours).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

[e] Schedule for triplicate ECGs during cycle 1 also applies in case of intra-subject dose escalation, regardless of actual study cycle.

[f] Two (2) sets of triplicate ECGs collected at Screening.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[h] The estimated glomerular filtration rate (eGFR) will be calculated based on institutional standards
[i] Premedication should be administered within 1 hour before the start of dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.
[j] Whole blood for peripheral blood mononuclear cells (PBMCs) collected prior to the dose on cycle 1 day 1 only if subject provides consent for collection of the pharmacogenetic (PG) sample.
[k] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

[o] Of note, for the eIV cohorts please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] μg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] μg over 24 hours), day 5 and day 8 will be short term IV infusions (~90 minutes each).

Table 20. Schedule of Assessments: Schedule C Cycle 2 (Days 1, 3, 5, 8, 12, and 19)

	Treatment Cycle 2																																			
Week	1																																			
Cycle Day	1											2	3[a]											4	5[a]											6
Hours	Pre-dose	Relative to start of dose											Pre-dose	Relative to start of dose											Pre-dose	Relative to start of dose										
		0	1[b]	2	3	4	6	8	12	16	20	24		0	1[b]	2	3	4	6	8	12	16	20	24		0	1[b]	2	3	4	6	8	12	16	20	24
GENERAL AND SAFETY ASSESSMENTS																																				
Hospitalization[c]	→																																			
Concomitant Medications	→																																			
Serious adverse events review	→																																			
Adverse events	→																																			
Physical Exam	X											X	X											X	X											X
ECOG	X																																			
Weight	X																																			
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X	X		X[b]	X	X	X	X	X	X	X	X	X
ECG triplicate measurement	X		X[b]										X		X[b]										X		X[b]									
LABORATORY ASSESSMENTS																																				
Coagulation	X							X				X	X											X	X											X
Hematology, Chemistry	X							X				X	X											X	X											X
Urinalysis	X												X												X											
[redacted]																																				
INVESTIGATIONAL PRODUCT DOSING																																				
AMG 427 dose[m]		X												X												X										
Premedication[f]	X												X												X											
BIOMARKER ASSESSMENTS																																				
[redacted]																																				
PK ASSESSMENTS																																				
AMG 427 PK[g]	X		X[b]				X					X	X		X[b]									X	X		X[b]									X
DISEASE & BIOMARKER ASSESSMENTS																																				
[redacted]																																				

	Treatment Cycle 2																										
Week	2																										
Cycle Day		8[a]										9	10	11	12[a]											13	14
Hours	Pre-dose	Relative to start of dose													Pre-dose	Relative to start of dose											
		0	1[b]	2	3	4	6	8	12	16	20	24	48	72		0	1[b]	2	3	4	6	8	12	16	20	24	48
GENERAL AND SAFETY ASSESSMENTS																											
Hospitalization[c]	→																										
Concomitant Medications	→																										
Serious adverse events review	→																										
Adverse events	→																										
Physical Exam	X											X	X	X	X												X
ECOG																											
Weight																											
Vital signs, pulse oximetry[d]	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X		X[b]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X
ECG triplicate measurement	X		X[b]												X		X[b]										
LABORATORY ASSESSMENTS																											
Coagulation	X											X	X	X	X												X
Hematology, Chemistry	X											X	X	X	X												X
Urinalysis	X														X												
[redacted]																											
INVESTIGATIONAL PRODUCT DOSING																											
AMG 427 dose[m]		X														X											
Premedication[f]	X														X												
BIOMARKER ASSESSMENTS																											
[redacted]																											
PK ASSESSMENTS																											
AMG 427 PK[g]	X		X[b]									X			X		X[b]									X	
DISEASE & BIOMARKER ASSESSMENTS																											
[redacted]																											

	Treatment Cycle 2														
Week	3														4
Cycle Day	19[a]											20	21	22	28
Hours	Pre-dose	Relative to start of dose													
		0	1[b]	2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS															
Hospitalization[c]															
Concomitant Medications	→														
Serious adverse events review	→														
Adverse events	→														
Physical Exam	X												X		X
ECOG															
Weight															
Vital signs, pulse oximetry[d]	X		X[b]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		X		X
ECG triplicate measurement	X		X[b]												
LABORATORY ASSESSMENTS															
Coagulation	X												X		
Hematology, Chemistry	X												X		X
Urinalysis	X														
[redacted]															
INVESTIGATIONAL PRODUCT DOSING															
AMG 427 dose[m]		X													
Premedication[f]	X														
BIOMARKER ASSESSMENTS															
[redacted]															
PK ASSESSMENTS															
AMG 427 PK[g]	X		X[b]				X					X	X	X	X
DISEASE & BIOMARKER ASSESSMENTS															
[redacted]															

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eIV = extended IV; IV = intravenous; PK = pharmacokinetic

[a] The Dose Level Review Team may recommend to change timing of D3/D5/D8/D12/D19 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly

[b] Collect assessments at the end of infusion (EOI). For the First-in-Human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~ 90 minutes, eIV~ 24 hours).

[c] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).

[d] Vital signs/pulse oximetry will also be assessed prior to subject`s discharge from hospital or leaves the clinic in order to detect possible signs and symptoms of infusion reactions.

[e] Time points for vital sign and pulse oximetry measurements after the end of dose time point apply only if the subject is still at the clinic at the time.

[f] Premedication should be administered within 1 hour before the start of dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.

[g] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.

[redacted]

[m] Of note, for the eIV cohorts please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] µg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] µg over 24 hours), day 5 and day 8 will be short term IV infusions (~ 90 minutes each).

Table 21. Schedule of Assessments: Schedule C Cycle ≥ 3 (Days 1, 3, 5, 8, 12, and 19)

	Treatment Cycle 3 and following																					
Week	1																					
Cycle Day	1											3[c]										
Hours	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20
GENERAL AND SAFETY ASSESSMENTS																						
Hospitalization[e]																						
Concomitant Medications	→																					
Serious adverse events review	→																					
Adverse events	→																					
Physical Exam	X											X										
ECOG	X																					
Weight	X																					
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
ECG triplicate measurement																						
LABORATORY ASSESSMENTS																						
Coagulation	X											X										
Hematology, Chemistry	X											X										
Urinalysis	X											X										
Urine Pregnancy Test																						
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 427 dose[q]		X											X									
Premedication[i]	X											X										
BIOMARKER ASSESSMENTS																						
[redacted]																						
PK ASSESSMENTS																						
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]								
DISEASE & BIOMARKER ASSESSMENTS																						
[redacted]																						

Week												2										
Cycle Day	5[c]											8[c]										
Hours	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20
GENERAL AND SAFETY ASSESSMENTS																						
Hospitalization[e]																						
Concomitant Medications	→																					
Serious adverse events review	→																					
Adverse events	→																					
Physical Exam	X											X										
ECOG																						
Weight																						
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
ECG triplicate measurement																						
LABORATORY ASSESSMENTS																						
Coagulation	X											X										
Hematology, Chemistry	X											X										
Urinalysis	X											X										
Urine Pregnancy Test																						
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 427 dose[q]		X											X									
Premedication[i]	X											X										
BIOMARKER ASSESSMENTS																						
[redacted]																						
PK ASSESSMENTS																						
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]								
DISEASE & BIOMARKER ASSESSMENTS																						
[redacted]																						

																							EOT	SFU[a]	LTFU[b]
Week												3											4		4 weeks post last dose of AMG 427 (+1 week)	Up to 2 yrs after 1st dose of AMG 427; every 8 weeks (±2 weeks)
Cycle Day	12[c]											19[c]											28			
Hours	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20	Pre-dose	0	1[d]	2	3	4	6	8	12	16	20				
GENERAL AND SAFETY ASSESSMENTS																										
Hospitalization[e]																										
Concomitant Medications	→																									X[f]
Serious adverse events review	→																									
Adverse events	→																									
Physical Exam	X											X												X	X	
ECOG																								X	X	
Weight																										
Vital signs, pulse oximetry[g]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X		X[d]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X	
ECG triplicate measurement																								X	X	
LABORATORY ASSESSMENTS																										
Coagulation	X											X												X	X	
Hematology, Chemistry	X											X											X	X	X	
Urinalysis	X											X												X		
Urine Pregnancy Test																									X[o]	
[redacted]																										
INVESTIGATIONAL PRODUCT DOSING																										
AMG 427 dose[q]		X											X													
Premedication[i]	X											X														
BIOMARKER ASSESSMENTS																										
[redacted]																										
PK ASSESSMENTS																										
AMG 427 PK[j]	X[k]		X[d]									X[k]		X[d]										X	X	
DISEASE & BIOMARKER ASSESSMENTS																										
[redacted]																										

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eIV = extended IV; EOT = End of Treatment; IV = intravenous; LTFU = long term follow-up; PK = pharmacokinetic; SFU = safety follow-up;

[a] The safety follow-up (SFU) visit occurs 4 weeks (+1 week) after the last infusion of AMG 427. For subjects enrolled in the escalation phase, this visit may also be the end of study (EOS) visit.

[b] The long term follow-up (LTFU) period may consist of a telephone call performed every 8 weeks (± 2 weeks) to assess disease status and anti-AML therapy(ies). LTFU applies only to subjects enrolled in the dose expansion phase. The last contact with a subject may also signify EOS. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen.**

[c] The Dose Level Review Team may recommend to change timing of D3/D5/D8/D12/D19 within a window of ± 1-3 days. In this case, timing of the following visits would be adjusted accordingly.

[d] Collect assessments at the end of infusion (EOI). For the First-in-Human cohorts: End of infusion time is defined as the time at which the total infusion is complete (end of investigational product AMG 427 and flush infusion). Collect assessments after total infusion time is complete (ie, short IV ~90 minutes, eIV~ 24 hours).

[e] See protocol Section 6.2.1.1 for details on hospitalization requirements and in case of dose step. Subjects should be monitored intensively for at least 4 hours after the start of dose for clinical signs (eg, fever, hypotension, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome (CRS).
[f] Collect anti-AML treatments only.
[g] Vital signs/pulse oximetry will also be assessed prior when the subject leaves the clinic in order to detect possible signs and symptoms of infusion reactions.
[h] Time points for vital sign and pulse oximetry measurements after the end of dose time point apply only if the subject is still at the clinic at the time.
[i] Premedication should be administered within 1 hour before the start of dose and prior to each step-up dose of AMG 427 dose to mitigate the risk for the prevention of CRS.
[j] Blood must not be drawn from the port catheter during investigational product infusion and for 5 minutes after the end of infusion. If sample processing/shipment is not logistically feasible for a certain time point (eg, in case it coincides with the weekend) this sample time point is not mandatory.
[k] For cycles 4 through cycle 12: ONLY predose PK samples are collected (predose: D1, D3, D5, D8, D12, D19). EOT and SFU also to be collected cycles 4 through 12.

[redacted]

[o] If applicable, urine pregnancy test required 4 weeks after the last dose of AMG 427.

[redacted]

[q] Of note, for the eIV cohorts please reference protocol details for dosing. Day 1 eIV will be over day 1 and 2 (eg, [redacted] µg dose will be infused over days 1 and 2 [48 hours]), day 3 eIV infusion will be over day 3 only (eg, [redacted] µg over 24 hours), day 5 and day 8 will be short term IV infusions (~90 minutes each).

Table 22. Schedule of Assessments: MRD+ Group Only - Whole Blood MRD Collection (Days 1, 3, 5, and 8)

MRD+ Whole Blood Collection (Day 1, 3, 5, 8)				
Cycle	Cycle 1		Cycle ≥ 2	EOT
Week	1		1	
Cycle Day	1	14	14	
Hours	Pre-dose			
Whole blood MRD (MRD cohort only)				
Whole blood MRD (MRD cohorts only)[a]	X[a]	X[a]	X[a]	X[a]

EOT = End of Treatment; MRD = minimal/measurable residual disease; MRD+ = minimal/measurable residual disease-positive

[a] MRD+ groups will follow all Schedule C (Table 16 through Table 21) for all collections. Additionally, MRD+ cohorts will collect whole blood MRD at the following timepoints for all cycles.

Table 23. Schedule of Assessments: MRD+ Group Only – Whole Blood MRD Collection (Days 1, 3, 5, 8, 12, and 19)

MRD+ Whole Blood Collection (Day 1, 3, 5, 8, 12, and 19)				
Cycle	Cycle 1		Cycle ≥ 2	EOT
Week	1	4	4	
Cycle Day	1	28	28	
Hours	Pre-dose			
Whole blood MRD				
Whole blood MRD (MRD cohorts only)[a]	X[a]	X[a]	X[a]	X[a]

EOT = End of Treatment; MRD = minimal/measurable residual disease; MRD+ = minimal/measurable residual disease-positive

[a] MRD+ cohorts will follow all Schedule C (Table 16 through Table 21) for all collections. Additionally, MRD+ cohorts will collect whole blood MRD at the following timepoints for all cycles.

7.2 General Study Procedures

A signed and dated IRB/IEC approved ICF must be obtained prior to performing any study-specific procedures including discontinuing standard therapy for observing a study washout period.

During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Table 10 to Table 23). Every effort should be taken to collect all biomarker and PK samples as described in the schedule of assessments. However, if sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a deviation from the protocol.

Subjects will be seen in the clinic for study evaluations. When electrocardiograms (ECGs), vital signs, blood sample collections, biomarker sample collections, and aspirate/biopsy sample collections occur on the same visit, ECGs and vital signs should be performed before samples (blood, biopsy/aspirate) are collected. Blood samples must not be taken/drawn from the catheter port used for AMG 427 infusion. If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration (see also Section 7.3.15). The time of blood sample collection must be recorded with the exact time of collection (do not use the time that the samples were frozen or any other time point).

The study specific manuals provide additional details regarding the requirements for these procedures.

Acceptable deviation windows are as follows:

- Infusion duration ± 10 minute window.
- ECGs, biomarker blood draws (cycles 1 – 3), vital signs (including pulse oximetry):
    - ± 15 minute window if collected within the first 24 hours (excluding the 24 hour sample) after the start of any dose
    - ± 2 hour window if collected between 24 hours and 3 days after the start of any dose
    - Assessments after day 3 but within 7 days post infusion start should be performed on the indicated study day, but are not required at a certain hour of the day
    - Assessments after day 7 have a ± 1 day window
- For R/R AML subjects, bone marrow assessments post treatment start: ± 3 days

- For MRD+ subjects, bone marrow assessments do not need to be repeated if done within 3 months prior to start of treatment with AMG 427. If more than 3 months have passed, discuss with medical monitor prior to performing.
- PK blood draws in cycles 1 - 3:
  - within 2 hours prior to infusion start
  - ± 15 minute window for samples taken after the end of each dose
  - Blood must not be drawn from the port catheter during infusion and for 5 minutes after the end of infusion. End of infusion (EOI) is defined as end of total infusion time (after investigational product and IV flush infusion).

For dosing visits a ± 1 - 3 day time window applies.

Local laboratories should be used for the following assessments: hematology, hematological bone marrow assessments, clinical chemistry, coagulation, urinalysis, hepatitis serology, and serum pregnancy tests. The following collections will be shipped to a central laboratory for analysis: blood samples for determination of serum concentrations of AMG 427 and presence of [redacted].
Refer to the laboratory manual for detailed collection, processing, and shipping procedures.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.1 Screening

After written informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening procedures must be performed within 14 days prior to start of investigational product administration, unless otherwise noted. The ICF may be signed earlier than 14 days prior to start of investigational product in case of washout times that have to be observed to meet eligibility criteria. Re-consent is necessary if the date of consent is longer than 14 days prior to the start of the first dose of AMG 427.

Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study. Subjects who do not meet the eligibility criteria within the 14-day screening period will not be eligible for enrollment. Subjects who are deemed ineligible will be documented as screen failures.

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation (up to a total of 2 times during the 14-day screening period) if necessary

before the subject is considered a screen failure. If any assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 10 to Table 23). Assessments that were performed as standard of care prior to signature of informed consent but within 14 days prior to start of treatment with AMG 427 can be used as screening assessments and do not need to be repeated to confirm subject eligibility. Hepatitis serology does not need to be repeated to determine eligibility if it was performed within 6 weeks prior to start of treatment with AMG 427.

- Confirmation that the ICF has been signed
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety
- Clinical evaluation
  - Physical examination as per standard of care (including medical/surgical history). Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Height and weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- Pulse oximetry
- ECG triplicate measurements (2 sets of triplicates)
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, serum pregnancy test (females only), and hepatitis serology
- Estimated glomerular filtration rate (eGFR)
- Bone marrow assessments
- Serious adverse event reporting
- Documentation of concomitant and rescue medications.

Re-screening:

A subject may be rescreened up to 3 additional times during the study at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the 14-day screening period.

Re-screened subjects must be documented as screen failed in the subject's medical record and subsequently documented as re-screened. Subjects will retain the same subject identification number assigned at the time of initial screening. Once the subject

is recorded as re-screened, a new 14-day screening window will begin. The following assessments do not have to be repeated during re-screening if they were performed as standard of care or during the initial screening attempt within the time frames specified below:

- Hepatitis serology does not need to be repeated if it was performed within 6 weeks prior to start of treatment with AMG 427
- Bone marrow assessments (except molecular panel, see last bullet) do not need to repeated if done within 4 weeks prior to start of treatment with AMG 427 as long as subject did not receive any anti-leukemic therapy in the interim
- Molecular panel on bone marrow does not need to be repeated if done within 3 months of starting AMG 427 therapy

7.2.2 Treatment

Treatment begins on day 1 (cycle 1 day 1) when the first dose of investigational product is administered to a subject.

After the mandatory hospitalization period (see Section 6.2.1.1), clinic visits may be conducted per institutional standard of care

The following procedures will be completed during the treatment period at the times designated in the Schedules of Assessments (Table 10 to Table 23).

Laboratory assessments that were done within 24 hours prior to treatment start do not need to be repeated at D1 prior to dose.

- Hospitalization (see Section 6.2.1.1 for minimum required hospitalization times)
- Investigational product doses (See Section 6.2.1.1 for details)
- Physical examination as per standard of care. Abnormal findings from the physical examination findings should be recorded in the events form.
- ECOG performance status
- Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement (1 set)
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis
- Biomarker assessments:

- AMG 427 PK sample collection
- [redacted]
- Bone marrow assessments
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant medications
- Contrast enhanced MRI or computed tomography (CT) scan (to be considered in case of CNS adverse event of grade ≥ 3 only, particularly in cases of confusion, disorientation or seizures)
- Receipt of protocol-required therapies (may include premedication)
- Pharmacogenetics sample (optional) collected pre-dose cycle 1 day 1
- For subjects to whom intra-subject dose escalation (see Section 7.2.2) applies:
  - ECG assessments should be performed as in cycle 1, regardless of actual study cycle
  - PK samples should be taken as in cycles 1 and 2, respectively, regardless of actual study cycle
  - All other assessments should be performed as per the schedule of assessments for the actual cycle.

7.2.3 End of Treatment Visit

The EOT visit will occur at the end of the last treatment cycle. For subjects who prematurely discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product was administered. The following procedures will be completed during the EOT visit as designated in the Schedules of Assessments (Table 10 to Table 23):

- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement (1 set)
- Laboratory assessments: hematology, chemistry, coagulation, and urinalysis
- Biomarker assessments:

[redacted]

- AMG 427 PK sample collection

[redacted]

- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant medications

7.2.4 Safety Follow-up Visit

The safety follow-up (SFU) visit is to be performed at least 4 weeks (or up to 7 days thereafter) after the last dose of AMG 427 or prior to the initiation of other AML therapy, whichever occurs earlier. **The safety follow-up period minimum is 30 days post last dose of investigational product.** All efforts should be made to conduct this visit including subjects who withdraw from treatment early. If it is not possible to conduct the SFU visit, documentation of the efforts to complete the visit should be provided in the source documents and noted as not done in the eCRF.

Subjects enrolled in the dose escalation phase who complete the safety follow-up visit will be considered to have completed the study.

The following procedures will be completed at the SFU visit as designated in the Schedules of Assessments (Table 10 to Table 23).

- Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
- ECOG Performance Status
- Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement (1 set)
- Laboratory assessments: hematology, chemistry, and coagulation
- Biomarker assessments:

- AMG 427 PK sample collection

- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant medications
- Bone Marrow/MRD assessment

7.2.5 Long-term Follow-up

After the safety follow-up visit all subjects in the expansion phase only will enter the long-term follow-up (LTFU). Subjects will be contacted by telephone to assess survival, disease status, and anti-AML therapy following the end of AMG 427 treatment. On-site visits are not required by all subjects. Contact for all subjects will be attempted every 8 weeks (± 2 weeks) following the safety follow-up visit, as applicable, until death, subject withdraws full consent, or up to a maximum of 2 years from the first dose of AMG 427, whichever occurs first.

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in Section 7.2**.**

7.3.1 Informed Consent

A signed ICF must be obtained from each subject prior to any study-mandated procedures.

7.3.2 Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact of the protocol-required therapy on biomarker variability and PK.

7.3.3 Medical History and Prior Therapy

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening up until the time of consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

Relevant medical history, including antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (resolved and ongoing) will be collected. AML history must date back to the initial diagnosis and any response duration must be recorded. The current toxicity grade will be collected for each condition that has not resolved. All prior cancer treatment therapies will be collected.

7.3.4 Concomitant Medications

Concomitant therapies **(including vaccines)** are to be collected from informed consent through the EOS. In case the screening period is shorter than 2 weeks (ie, informed consent is obtained less than 2 weeks prior to start of study treatment), concomitant

medications for which washout periods have to be observed (refer to Section 4.2, Section 6.3, and Section 6.9) are to be collected starting 2 weeks prior to start of study treatment. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.3.5 Physical Examination

A complete physical examination as per standard of care (rectal and vaginal examination not required) will be performed by the investigator or designee at screening and at the time points specified in the Schedules of Assessments (Table 10 to Table 23). The physical examination will include general appearance, including examination of the skin, spleen, and signs of extramedullary leukemia and respiratory, cardiovascular, musculoskeletal, and neurological systems.

The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal physical examination findings found during screening should be reported on the Medical History eCRF. Abnormal physical examination findings found after the subject has provided consent will be reported on the Event eCRF.

7.3.6 ECOG Performance Status

Subjects will be graded according to the ECOG Performance Status (see Appendix F).

7.3.7 Height Measurements

Height in centimeters should be measured without shoes at screening.

7.3.8 Weight Measurements

Weight in kilograms should be measured without shoes.

7.3.9 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Record all measurements on the vital signs eCRF.

The subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

The location for temperature measurement selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

7.3.10 Pulse Oximetry

Oxygen saturation will be measured using a standard pulse oximeter. The subject must be in a rested and calm state for at least 5 minutes before pulse oximetry assessments are completed.

7.3.11 Electrocardiogram Performed in Triplicate

The subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

ECGs should be performed in a standardized method, in triplicate, (ie, approximately 30 seconds apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

Electrocardiograms will be performed as follows:

- Baseline ECGs will be collected ≥ 30 minutes apart, with each baseline ECG in triplicate (ie, triplicate must be done approximately 30 seconds apart)
  - 2 sets collected at screening, and
  - 1 set collected pre-dose on cycle 1 day 1 [ie, total ≥ 9 ECGs])
- Triplicate ECGs at time points after dosing.

The investigator or designated site physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader for processing per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

Standard ECG machines should be used for all study-related ECG requirements.

7.3.12 Clinical Laboratory Tests

The tests listed below in Table 24 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Table 10 to Table 23). The test results are to be recorded on the eCRFs. Missed test(s) that are not done must be reported as such on the eCRFs.

Additional procedures (eg, collection of an unscheduled blood sample to measure cytokine levels) deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

A serum pregnancy test will be performed locally at each site at the screening visit on all females unless they are surgically sterile or ≥ 2 years postmenopausal.

Table 24. List of Analytes

Local Laboratory					Central Laboratory
Chemistry	Hematology	Urinalysis	Coagulation	Other Labs	
Sodium Potassium Bicarbonate or Total CO2 Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Total bilirubin ALP AST ALT Amylase Lipase CRP LDH Uric Acid eGFR (per institutional formula)	Hemoglobin Hematocrit Platelets White Blood Cells Total Neutrophils Segmented Neutrophils Lymphocytes Monocytes Bands/Stabs Eosinophils Basophils Blasts Absolute neutrophil count Myeloblasts **Erythrocyte sedimentation rate (ESR)** **Ferritin**	Specific gravity pH Blood Protein Glucose Bilirubin Ketones Microscopic exam (performed at the discretion of the investigator)	PT aPTT INR Fibrinogen D-Dimer Antithrombin	Pregnancy test[a] Serology (HepB and HepC)[b] Bone marrow assessments[c,d] – morphology – immunophenotype – cytogenetics – molecular panel – MRD	[redacted] AMG 427 PK samples Pharmacogenetics sample Biomarkers [redacted]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase;; CRP = C-reactive protein; HepB = hepatitis B; HepC = hepatitis C; [redacted] INR = international normalize ratio; LDH = lactate dehydrogenase; [redacted]; MRD = Minimal/Measurable Residual Disease; PK = pharmacokinetic; PT = prothrombin time; [redacted]

[a] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal. Urine pregnancy test will be performed 4 weeks after the last dose of AMG 427 (if applicable).

[b] Serology may include: HepBsAg (hepatitis B surface antigen) and HepCAb (hepatitis C antibody).

[c] A screening molecular panel on bone marrow is required (NPM1, FLT3 ITD/TKD, IDH1/2, CEBPA, etc.). Molecular panel done within 3 months of study day 1 is acceptable.

[d] Post-treatment bone marrow assessment is optional if the absolute peripheral blood blast count is ≥ 20% (screening bone marrow is still required).

7.3.13 Events

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF as specified in Sections 9.2 and 9.1.1, respectively. The severity of all events will be graded according to CTCAE, version 4.0 (Appendix A) unless specified otherwise. Exception: CRS will be graded according to the adopted grading system referenced in Lee et al, 201**9** (see Table 6) **and ICANS will be graded according to the criteria referenced in the publication by Lee et al, 2019 (see Table 8)**.

7.3.14 Head CT or Cranial MRI

A contrast-enhanced MRI or CT scan of the head should be considered for subjects who experienced a CNS event grade **2** or higher, particularly in cases of confusion, disorientation or seizures.

7.3.15 Pharmacokinetic Blood Sampling

Blood samples will be obtained for determination of serum concentrations of AMG 427 at the time points specified in the Schedules of Assessments (Table 10 to Table 23). Blood must not be drawn from the port catheter during investigational product infusion and for at least 5 minutes after the end of infusion. End of infusion is defined as end of total infusion time (after investigational product and IV flush infusions). If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. However, the preference is for PK samples to be drawn peripherally during infusion. Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

Table 25. Bone Marrow Collections

Test	Time point		
	Screening	**D14 (for cohorts receiving D1, ± D3 & 5 doses)/D28 (for cohorts receiving D1, ± D3, 5, 8, 12, 19 doses) for all cycles**	**Unscheduled**
Bone marrow aspirate	Required	Required (unless peripheral blood absolute blast count 20%, in which case bone marrow assessments are optional).	As needed (eg, if infusion-free period is prolonged beyond 4 weeks for cytopenia, bone marrow aspirate must be performed before starting next cycle of AMG 427
Bone marrow biopsy	Required if aspirate is inadequate (eg, no spicules seen); optional if aspirate is adequate	Optional	Optional
Conventional cytogenetics	Required	Optional	Optional
Immunophenotype (including FLT3/CD135)[a]	Required on BM aspirate	Required on BM aspirate/peripheral blood blasts	Required on BM aspirates/peripheral blood blasts
Molecular panel (NPM1, FLT3 ITD/TKD, IDH1/2, CEBPA etc.)	Required on BM aspirate, within 3 months of day 1 is acceptable	Optional	Optional
Minimal/Measurable residual disease assessment	[redacted]	Required on BM aspirates only for subjects in CR	Required on BM aspirates only for subjects in CR
	Required for MRD+ AML subjects, only if not done within 3 months of enrollment (at local and central laboratory).		
[redacted]			

AML = Acute Myeloid Leukemia; BM = bone marrow; C = cycle; CR = complete response; MRD = minimal/measurable residual disease; MRD+ = minimal/measurable residual disease-positive; R/R = relapsed/refractory; SOA = schedule of assessments

[a] All disease/blast assessments must be confirmed by flow-cytometry based immunophenotype (a complete "AML flow panel" per institutional practices must be performed). This assessment may include FLT3 (CD135) expression (% and mean fluorescent intensity) on the myeloblasts.

[redacted]

Bone marrow assessments will be performed for the following:

- Morphology and immunophenotype to confirm eligibility at screening and response to treatment
- Standard cytogenetics – mandatory at screening only
- Immunological phenotyping to verify myeloid leukemia and assessments of MRD (if applicable) and [redacted]
- [redacted]

See Section 7.2.1 for guidelines for re-screening.

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

7.5.2 Assessment of MRD

The term MRD refers to the 'occult' low amount of leukemia that may persist during remission in the absence of clinical or hematological evidence of disease. Recently, the level of MRD was established as a prognostic factor that predicts relapse. MRD detection in AML using polymerase chain reaction (PCR) based techniques for molecular markers is applicable only in a minority of cases. Immunophenotypical detection of MRD is analyzed in 1 of 2 ways: (a) leukemia-associated immunophenotype (LAIP) or (b) deviation from normal maturation. The first is based upon the presence of so called LAIPs, which are unusual or aberrant immunophenotypes that distinguish leukemic cells from normal hematopoietic cells. The second, deviation from normal maturation, relies upon immunophenotypic deviation relative to normal bone marrow maturation. In this study, we will utilize the deviation from normal maturation method of MRD detection, as determined by a board-certified hematopathologist. This method relies upon cross-lineage antigen expression (eg, the expression of lymphoid markers on myeloid cells), asynchronous antigen expression (eg, the coexpression of early markers with mature myeloid markers), overexpression of antigens (eg, relatively high expression levels of particular myeloid or lymphoid markers), and/or ectopic expression (eg, the expression of particular antigens that normally are not expressed on hematopoietic cells). At diagnosis, the immunophenotypic deviation relative to normal bone marrow maturation is identified, and this diagnostic immunophenotype is used as a starting point to follow the discrete population having an immunophenotype different from normal bone marrow. Deviation

from normal maturation has an advantage over the LAIP method of MRD detection in that it has improved sensitivity through population identification and it is less sensitive to immunophenotypic instability.

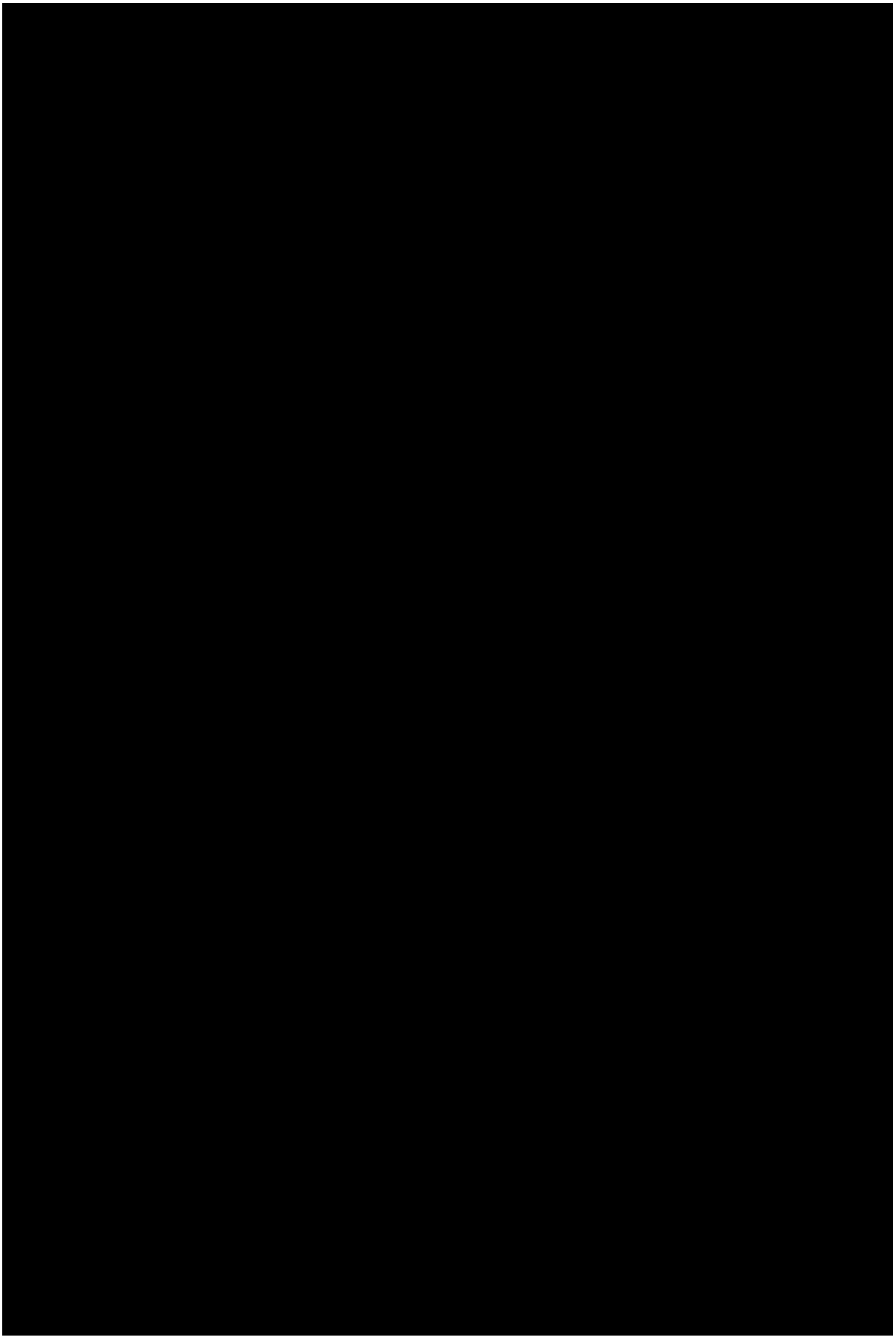
The method of MRD detection is quite easy to perform and is sensitive, with a detection ability of 1 malignant cell among 1,000 to 10,000 normal cells, but it requires detailed immunophenotypical knowledge of normal bone marrow cell differentiation. Bone marrow after different courses of therapy, stem cell transplants, and sequential follow-up bone marrow sampling have been used for MRD assessment.

In this study, MRD assessments will be utilized as both an eligibility/inclusion criteria in the MRD+ cohort, as well as an additional efficacy endpoint for all cohorts. [redacted]. For subjects enrolling in MRD+ group, bone marrow sample for MRD assessment is required for both local and central testing (except at screening visit for subjects with historical test result available < 3 months from start of treatment).

7.5.2.1 MRD Testing for Screening/Eligibility for MRD+ Group

For subjects to be eligible for study participation in MRD+ groups, bone marrow MRD assessment is required prior to enrollment to establish MRD status; local testing is sufficient for enrollment. Collection of bone marrow aspirate following local standard of care procedure for MRD testing is not expected to present any additional risk to the health, safety, and welfare of the subject. Screening for MRD will be conducted using an investigational diagnostic or validated local test/assay at a CLIA certified laboratory (for US only) agreed upon by the Sponsor; local testing is sufficient for the enrollment decision if the test result is from ≤ 3 months from the start of treatment. If new local testing is performed during screening, additional bone marrow aspirate from the same bone marrow pull is required to be sent for exploratory testing at central lab for these subjects.

[redacted]



[redacted]

[redacted]

7.7 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of AML and/or to identify subjects who may have positive or negative response to AMG 427. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.8 Sample Storage and Destruction

Any blood, biomarker, PK, cytogenetic, and bone marrow aspirate and biopsy samples collected according to the Schedule of Assessments (Table 10 to Table 23) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand AML, the dose response and/or prediction of response to AMG 427, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are

not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments

(Table 10 to Table 23) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and device related events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

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

- Confirmed disease progression as defined by revised IWG response criteria (Appendix E) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition
- Protocol specified criteria:
- Proceeding to HSCT

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

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

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

Every increase in severity of an adverse event needs to be recorded. Decrease in severity only has to be recorded for DLTs and adverse events that lead to interruption of treatment/delay of a subsequent dose.

For situations when an adverse event or serious adverse event is due to AML, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer).

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

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

9.1.2 Serious Adverse Events

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

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

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

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

9.1.3 Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 6.7 for the list of Amgen medical devices).

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include**, but are not limited to,** adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

A combination product is a product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the time of consent through **30 days after** the **last day** of the **dosing interval of investigational product/safety** follow-up visit **(whichever occurs later)**, are reported using the Event**s** CRF. Adverse events will be collected up to the safety follow up visit.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- **Assessment of seriousness,**
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to investigational products or study procedure/activity, and
- Action taken.

The adverse event grading scale used will be the CTCAE, version 4.0. The grading scale used in this study is described in Appendix A. Exception: CRS will be graded according to the guidelines provided in Table 6 (based on the adopted grading system referenced in Lee et al, 201**9**) **and ICANS will be graded according to the guidelines provided in Table 8 (based on the grading system referenced in the publication by Lee et al, 2019)**.

The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product, and/ or study procedure/activity?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory

findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through **30 days after the last day of the dosing interval of investigational product/safety follow-up visit, whichever occurs later,** are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's awareness of the event via the Event**s** CRF.

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

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

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

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to

Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

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

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

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

During the Long Term Follow-up period, if the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 9.2.1.2) is complete, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF.

After End of Study, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product. If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

9.2.1.4 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event case report form (CRF) page.

It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

9.2.1.5 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.1.6 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy, and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.1.7 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking AMG 427 report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 4 weeks after the last dose of AMG 427.

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

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

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

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

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 30 days after the last dose of protocol-required therapies.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

Safety:

- Dose limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and treatment-related adverse events (TRAEs)

Secondary Endpoints:

- AMG 427 PK parameters including, but not limited to, maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC), and if feasible, half-life ($t_{½}$) of AMG 427
- Efficacy parameters for R/R AML: subject response to treatment with AMG 427 (response defined as complete response/remission [CR]/ complete response/remission with incomplete recovery of peripheral blood counts [CRi], morphologic leukemia-free state, partial remission [per modified IWG criteria]), complete response/remission with partial hematologic recovery (CRh), and duration of response (duration of response will only be measured for subjects treated with the dose and schedule of the expansion cohort)
- Efficacy parameters for MRD+ AML: subject response to treatment with AMG 427 (response refers to conversion from MRD+ status to MRD- status), relapse free survival and overall survival (relapse free survival, and overall survival will only be measured for subjects in expansion cohort)

Exploratory Endpoints:

[redacted]

[redacted]

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 427.

The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.3 for definition). The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.3 for definition).

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

10.1.3 Covariates and Subgroups

The relationship of covariates to efficacy endpoints will be explored if appropriate.

[redacted]

Subgroup analysis for those treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

10.2 Sample Size Considerations

It is anticipated that approximately 2**0**0 subjects will be enrolled in this study. Approximately 1**1**0 subjects will be enrolled in the dose escalation cohorts (FIH: N = **90**, Etanercept substudy **(CLOSED)**: N = 25, MRD+: N = 10, eIV: N = 10) and 90 subjects will be enrolled in the dose expansion cohorts (FIH: N = 40, MRD+ AML: N = 50).

The sample size in the dose escalation is based on practical considerations and it is consistent with conventional oncology studies with the objective to estimate the MTD. With 2 subjects per cohort, there is a 19% to 55% probability of observing at least 1 DLT. With 3 subjects per cohort, there is a 27-70% probability of observing at least 1 DLT if the true DLT rate is 10-33% and with 4 subjects per cohort, there is a 34-80% probability.

In the dose expansion cohort, a subject number of 40 will provide an 87% probability of observing at least 1 adverse event with 5% incidence rate and 99% probability of observing at least 1 adverse event with 10% incidence rate. A subject number of 50 will provide a 92.3% probability of observing at least 1 adverse event with 5% incidence rate and 99.5% probability of observing at least 1 adverse event with 10% incidence rate. These probabilities will be 64% and 88% respectively with a subject number of 20. An exact 80% binomial confidence interval (CI) will be provided for response rate. With the 20 subjects and 20% response rate, the expected 80% CI would be 9% to 36%. With 40 subjects and 20% response rate, the expected 80% CI would be 12% and 30%. With 50 subjects and 40% response rate, the expected 80% CI would be 30.6% and 50.1%.

10.3 Adaptive Design

During dose expansion, Amgen will conduct evaluations of the ongoing DLT event rate and the ongoing overall response rate.

Safety Stopping Rules during Dose Expansion:

During dose expansion, Amgen will conduct evaluations of the ongoing DLT event rate to assess if the threshold for pausing enrollment has been reached. If these stopping rules are met, then enrollment to the dose expansion will be paused pending a review of safety data and available pharmacokinetic, pharmacodynamics, and efficacy data by the DLRT. This review may result in early termination of the study, notification to Health Authorities, or may result in re-initiation of enrollment. The DLRT may implement additional measures, as appropriate, to reduce the risk of toxicity or to adapt and manage the toxicity. The stopping rules to pause enrollment use a Bayesian approach proposed by Thall, et al (1995); enrollment to dose expansion will be halted if the posterior probability that the **DLT** rate is greater than 20% is $> 80\%$. The stopping boundaries assuming a prior distribution of Beta (0.40, 1.60) are presented in Table 26 and the operating characteristics with pre-specified batch size of 6 new subjects per batch are presented in Table 35. The evaluations could occur more frequently if necessary to address emerging safety concerns.

Table 26. Stopping Boundary for Dose Expansion With Posterior Probability of 80% DLT Limit of 20%

Number of subjects	Pause study enrollment if observing the number of these many **DLT** events
6	≥ 3
12	≥ 4
18	≥ 6
24	≥ 7
30	≥ 9
36	≥ 10
40	R/R AML expansion cohort completes
42	≥ 11
48	≥ 13
50	MRD+ AML expansion cohort completes

AML = acute myeloid leukemia, MRD+ = minimal/measurable residual disease-positive, R/R = relapsed/refractory.

Table 27. Operating Characteristics With Batch Size of 6 Subjects

	R/R AML		MRD+ AML	
True **DLT** rate	Probability of early stopping of dose expansion	Average dose expansion sample size*	Probability of early stopping of dose expansion	Average dose expansion sample size*
0.10	3.8%	38.9	3.9%	48.**5**
0.20	34.0%	31.5	37.8%	37.8
0.25	58.2%	25.6	64.9%	29.4
0.30	78.9%	19.9	85.5%	21.6
0.35	91.6%	15.4	95.7%	**16.0**
0.40	97.4%	12.2	99.1%	12.**3**
0.50	99.9%	8.7	100%	8.7

AML = acute myeloid leukemia, MRD+ = minimal/measurable residual disease-positive, R/R = relapsed/refractory.

* The average dose expansion sample size assumes early termination of the study whenever the rules to pause study enrollment are met.

Efficacy Futility Rules during Dose Expansion:

During dose expansion, Amgen will conduct evaluations of the ongoing overall response rate to assess if the threshold for early trial termination for futility has been reached. For R/R AML, a response consists of any of the following efficacious outcomes: **CR**, **CR** with incomplete recovery of peripheral blood counts (CRi), morphologic leukemia-free state, partial remission and complete response/remission with partial hematologic recovery (CRh). An overall response rate less than 15% is considered

insufficient efficacy. Amgen proposes stopping enrollment to the dose expansion cohorts early if any of the following occurs.

- None of the initial 12 subjects treated experience a response
- 2 or fewer of the initial 18 subjects treated experience a response
- 3 or fewer of the initial 24 subjects treated experience a response

Using these futility stopping rules, Table 28 shows the probability of early stopping and the average sample size in dose expansion.

Table 28. Probability of Early Stopping and the Average Sample Size in Dose Expansion

True overall response rate	Probability of early stopping after 12 or fewer subjects	Probability of early stopping after 18 or fewer subjects	Probability of early stopping after 24 or fewer subjects	Average sample size
0.05	0.54	0.94	0.98	15.5
0.10	0.28	0.74	0.82	20.7
0.15	0.14	0.49	0.58	27.0
0.20	0.07	0.28	0.34	32.5
0.30	0.01	0.06	0.07	38.3

[redacted] A conversion rate from MRD+ to MRD- < 25% is considered insufficient efficacy. Amgen proposes stopping enrollment to the dose expansion cohorts early if any of the following occurs:

- 2 or fewer of the initial 12 subjects treated experience a response
- 4 or fewer of the initial 18 subjects treated experience a response
- 5 or fewer of the initial 24 subjects treated experience a response

Using these futility stopping rules, Table 29 shows the probability of early stopping and the average sample size in dose expansion.

Table 29. Probability of Early Stopping and the Average Sample Size in Dose Expansion

True overall response rate	Probability of early stopping after 12 or fewer subjects	Probability of early stopping after 18 or fewer subjects	Probability of early stopping after 24 or fewer subjects	Average sample size
0.05	0.98	1.00	1.00	12.1

0.15	0.74	0.90	0.92	16.2
0.25	0.39	0.56	0.60	28.7
0.35	0.15	0.23	0.24	41.4
0.45	0.04	0.06	0.06	47.7

Siltuximab Safety Stopping Rules:

Amgen will conduct evaluations of the treatment and outcome of the CRS events treated with siltuximab on an ongoing basis to assess if the threshold for pausing siltuximab treatment has been reached as outlined in the table below. If these stopping rules are met, an adhoc DLRM will be triggered to review safety data and available pharmacokinetic, pharmacodynamics, and efficacy data. If recommended by DLRT, the use of siltuximab will resume. The stopping rules to trigger an adhoc DLRM to review siltuximab treatment use a Bayesian approach proposed by Thall et al (1995); an adhoc DLRM will be triggered if the posterior probability that the CRS progression to grade 3 rate is greater than 20% is > 80% or the posterior probability that the CRS progression to grade 4 rate is greater than 7.5% is > 80%; or observation of any grade 5 CRS after the event has been treated with siltuximab. The stopping boundaries presented below assume a prior distribution of Beta (0.4, 1.6) for progression to grade 3 CRS and a prior distribution of Beta (0.15, 1.85) for progression to grade 4 CRS. The evaluations could occur more frequently if necessary to address emerging safety concerns. If the triggered ad hoc DLRM coincide with regular DLRM, they may be combined.

	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
Number of Subjects Treated with Siltuximab	**Or this number of subjects with severity of CRS progressed to Grade 3 after being treated with siltuximab**	**Or this number of subjects with severity of CRS progressed to Grade 4 after being treated with siltuximab**
5	≥ 3	≥ 2
10	≥ **4**	≥ **2**
15	≥ **5**	≥ 3
20	≥ **6**	≥ **3**
25	≥ **7**	≥ **4**
30	≥ **9**	≥ **4**
35	≥ **10**	≥ **5**
40	≥ **11**	≥ **5**

CRS = cytokine release syndrome; DLRM = dose level review meeting

10.4 Planned Analyses

The following data analyses are planned: (1) the primary analysis after all dose-escalation and dose-expansion subjects had the opportunity to receive up to 12 cycles of treatment or terminated the study early, and (2) the final analysis after all subjects have ended the study.

10.4.1 Interim Analyses and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. Based on accumulating toxicity information, BLRM will be used to make dosing recommendations. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation decisions. As a sensitivity analysis, a 1-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

Ad-hoc interim analysis for efficacy parameters will be conducted after dose escalation is completed. Once preliminary MTD and R2PD is established, FDA will be provided with brief interim results of the dose escalation phase.

10.4.2 Dose Level Review Team (DLRT)

DLRMs will be held to review data, monitor safety, and make decisions on dose escalation/change, or changes in pre-medication. If a cohort extension of up to 6 subjects initiates, a DLRT meeting will be conducted after completion of the Japan cohort extension. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: early development leader, global safety officer or designee, clinical study manager, biostatistician, PK scientist (optional), and other functional area representatives as appropriate. The following members are responsible for DLRT recommendations: investigators, Amgen medical monitor, and global safety officer or designee. All available study data, including data collected after the initial DLT window, and including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, and PK/PD information will be reviewed. In addition to DLTs, all $\geq$ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT recommendations. Modeling of available potential safety risk data (eg, for

thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

A quorum as defined below must be in attendance for the DLRM. The quorum is defined as > 50% of the responsible members or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg, e-mail] of the investigator`s vote), as well as > 50% of Amgen representatives listed above. The early development leader or designee must attend for the quorum to be reached. The DLRM will be rescheduled if a quorum is not reached.

The following recommendations will be made by the DLRT:

- dose escalation/de-escalation decisions
- administration of additional doses on D12/D19 of a cycle
- number of subjects per cohort
- continuation, delay or termination of dosing
- implementation of dose step(s)
- change of the D1/D3/ D5/D12/D19 dosing scheme within the pre-specified window of ± 1-3 days
- extension of the treatment-free interval between treatment cycles
- If grade 5 event is fatal and suspected to be related to investigational product, study may be put on hold if recommended by DLRM.

Additionally, the DLRT will review safety data for each of the Japan cohort extension subjects, at regular intervals as part of ongoing DLRMs.

Subjects' cytogenetic profiles (eg, potentially higher cytokine release in monocytic AML) should be taken into consideration for DLRT recommendations.

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT once every 6th subject has at least completed their first treatment cycle plus 2 weeks or dropped out of treatment/study, whichever occurs earlier. Ad hoc meetings may be convened any time in case of important safety events.

10.4.3 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject had the opportunity to receive up to 12 cycles of treatment or terminated the study early.

10.4.4 Final Analysis

A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study. Primary and final analysis may be combined in case all subjects have ended study close to the time point of the primary analysis.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. A 2-parameter BLRM will be used to estimate the dose-toxicity relationship. See Appendix H for the description of the 2 parameter-BLRM design.

10.5.2 Primary Endpoint

Safety Endpoints

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 427.

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

Adverse Events

Subject incidence of all treatment-emergent **and treatment-related** adverse events will be tabulated by system organ class**,** preferred term**, and worst severity grade**. The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

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

Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be presented and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory

data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

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

Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized and the number and percentage of subjects in each cohort will be summarized.

Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each cohort will be summarized.

All on-study ECG data will be presented, and select parameters of interest may be plotted.

10.5.3 Secondary Endpoints

10.5.3.1 Pharmacokinetics Data Analysis

For AMG 427, pharmacokinetic parameters will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 427 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

10.5.3.2 Efficacy Endpoint Analyses

For R/R AML, the proportion of subjects with a CR/CRi/morphologic leukemia-free/CRh/Partial remission state with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by cohort and tabulated for all subjects treated at the MTD. A Kaplan Meier curve may be presented for duration of response with estimates for rates and 80% CI at selected weeks for subjects in expansion cohort. For MRD+ AML, the MRD conversion rate will be presented with corresponding exact 80% CI and tabulated by cohort and for all

subjects treated at the MTD. A Kaplan Meier curve may be presented for relapse free survival and overall survival with estimates for rates and 80% CI at selected weeks for subjects in expansion cohort. [redacted] will be considered exploratory.

10.5.4 Exploratory Endpoints

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen study manager to the investigator. The written ICF is to be prepared in the language(s) of the potential subject population.

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

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document**, that Amgen distributes to the site**. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed CRF, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s), and/or medical device(s) documentation.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 10 to Table 23), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

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

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the

work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE version 4 will be used for grading all adverse events (other than cytokine release syndrome **[see Table 6] and ICANS will be graded according to the criteria referenced in the publication by Lee et al, 2019 [see Table 8]**). The CTCAE can be found at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for potential signals of drug-induced liver injury (DILI), cases of concurrent AST or ALT and TBIL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.1.2.

Additional Clinical Assessments and Observation

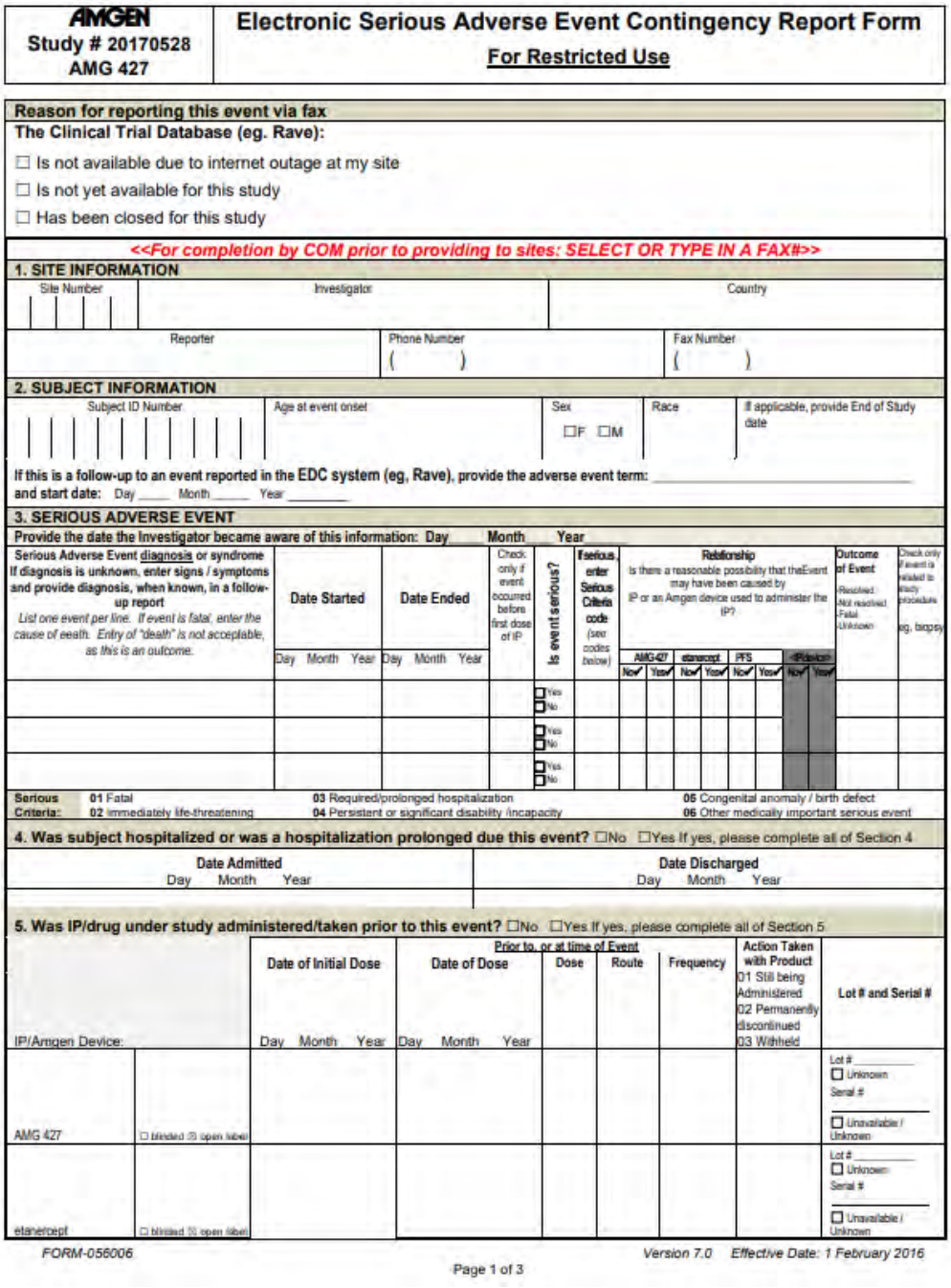
All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who experience AST or ALT elevations $>$ 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBIL $>$ 2x ULN or INR $>$ 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBIL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - CPK, haptoglobin, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBIL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Serious Adverse Event Form and eSerious Event Contingency Form



AMGEN
Study # 20170528
AMG 427

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 427 (No / Yes)	etanercept (No / Yes)	PFS (No / Yes)	<Placebo> (No / Yes)	Outcome of Event (Resolved / Not resolved / Fatal / Unknown)	Check only if event is related to study procedure (eg, biopsy)
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product (01 Still being Administered; 02 Permanently discontinued; 03 Withheld)	Lot # and Serial #
AMG 427	☐ blinded ☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
etanercept	☐ blinded ☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

AMGEN Study # 20170528 AMG 427	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

PFS	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170528 AMG 427	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170528

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐ No ☐Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20170528

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix D. World Health Organization Classification for Acute Myeloid Leukemias

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

Abnormal promyelocytes in acute promyelocytic leukemia, promonocytes in AML with monocytic differentiation and megakaryoblasts in acute megakaryocytic leukemia are considered blast equivalents. Patients with APML are not eligible for this study.

First, AML should be classified as AML with recurrent cytogenetic abnormalities. If this is not applicable the leukemia is classified as AML with multilineage dysplasia or therapy related and if this subtype is also not applicable as AML not otherwise categorized.

Acute Myeloid Leukemia and Related Precursor Neoplasms, and Acute Leukemias of Ambiguous Lineage (WHO, 2016)

Categories
Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
APL with PML-RARA*
AML with t(9;11)(p22;q23); MLLT3-KMT2A
AML with t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
Provisional entity: AML with BCR-ABL1; AML with mutated NPM1
AML with biallelic mutation of CEBPA
Provisional entity: AML with mutated RUNX1
Acute myeloid leukemia with myelodysplasia-related changes‡
Therapy-related myeloid neoplasms§
Acute myeloid leukemia, not otherwise specified
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)

Footnote defined on next page

Categories
Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)
Myeloid proliferations related to Down syndrome Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder) Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage Acute undifferentiated leukemia Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1‖ Mixed phenotype acute leukemia with t(v;11q23); KMT2A rearranged Mixed phenotype acute leukemia, B/myeloid, NOS Mixed phenotype acute leukemia, T/myeloid, NOS

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Adopted from Arber et al, 2016; for a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.

* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13; q12); *NUMA1-RARA*;AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5BRARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

† Other translocations involving *MLL* should be reported accordingly: for example, AML with t(6;11)(q27;q23); *MLLT4-MLL*; AML with t(11;19)(q23;p13.3); *MLLMLLT1*; AML with t(11;19)(q23;p13.1); *MLL-ELL*;AML with t(10;11)(p12;q23); *MLLT10-MLL*.

‡ More than 20% blood or marrow blasts *AND* any of the following: previous history of myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasm (MDS/MPN); myelodysplasia-related cytogenetic abnormality (see below); multilineage dysplasia; *AND* absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities; cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are:

- Complex karyotype (defined as 3 or more chromosomal abnormalities).
- Unbalanced changes: _7 or del(7q); _5 or del(5q); i(17q) or t(17p); _13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
- Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3; q21.1); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34).

§ Cytotoxic agents implicated in therapy-related hematologic neoplasms: alkylating agents; ionizing radiation therapy; topoisomerase II inhibitors; others.

‖ BCR-ABL1–positive leukemia may present as mixed phenotype acute leukemia, but should be treated as BCR-ABL1–positive acute lymphoblastic leukemia.

Appendix E. Revised International Working Group Response Criteria

Category	Definition
Complete remission (CR)[1]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L; platelet count > 100 x 10^9/L; independence of red cell transfusions
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L) or thrombocytopenia (< 100 x 10^9/L)
Morphologic leukemia-free state[3]	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR[4]	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR[5]	No standard definition; depends on molecular target

Treatment Failure Criteria

Category	Definition
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/III trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving > 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring > 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring > 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available Patients who do not complete the first course of therapy
Relapse[6]	Bone marrow blasts > 5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular or cytogenetic relapse	Reappearance of molecular or cytogenetic abnormality

[1] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat examination after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[2] The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CR_i patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

[3] This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

[4] Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.

[5] As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 104 copies of ABL1 in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.

[6] In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

[#] CRh (complete response/remission with partial hematologic recovery) will also be reported as an outcome measure. CRh is defined as ≤ 5% blasts in bone marrow, no evidence of circulating blasts or extramedullary disease and partial recovery of peripheral blood counts (platelets > 50,000/μL, hemoglobin ≥ 7g/dL and absolute neutrophil count > 500/μL).

Progressive Disease*

Progressive disease for patients with AML is defined as:

- Greater than 50% increase in bone marrow blasts from the best assessment and at least 20% marrow blasts.
- Greater than 50% increase in the peripheral blood absolute blast count and at least an absolute blast count of 1000/cmm.
- Development of extramedullary disease. If the patient has extramedullary disease at baseline, then the development of a new site of disease.
- In patients who present with a bone marrow blast percentage sufficiently high to preclude the ability to determine disease progression by a $>$ 50% increase in the marrow blast percentage, then disease progression will be determined by peripheral blood criteria or the development of new sites of extramedullary disease.

* Patients may remain on study treatment if the investigator believes the patient is deriving some benefit.

Relapse Criteria

Relapse after complete remission **(CR)** for patients with AML is defined as:

- recurrence of blasts in the marrow of $\geq$ 5% (excluding increased blasts in the context of regenerating marrow)
- recurrence of leukemic blasts in the peripheral blood
- recurrence of leukemia at an extramedullary site
- recurrence of pre-treatment characteristic signs of morphological dysplasia
- recurrence of Auer rods

These response criteria were published in the 2010 paper, "Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet" (Dohner et al, 2010), and are based on Revised IWG recommendations published in 2003 (Cheson et al, 2003).

Appendix F. Performance Status According to Eastern Cooperative Oncology Group (ECOG) Scale

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

Source: Oken MM, Creech RH, Tormey DC et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649-655

Appendix G. 2017 ELN Risk Stratification by Genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−E or del(5q); −or −or del(5q);
	Complex karyotype,§ monosomal karyotype||
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

* Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (< 0.5); high, high allelic ratio (≥ 0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.[57-59,77]

‡ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

|| Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).[116]

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Appendix H. Two-Parameter BLRM Design

A 2-parameter Bayesian logistic regression model (BLRM, Neuenschwander et al, 2008) is used to guide dose escalation. The MTD target Toxicity Probability Interval (TPI) for DLT is (0.20, 0.33) and TPIs of (0.33, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

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

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

A bi-variate normal prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at [redacted] μg is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose ([redacted] μg) is 0.05. Additionally, the prior is such that p_i is approximately 0.05 for the [redacted] μg dose and 0.25 for the reference dose. Once the [redacted] μg is deemed safe by Dose Level Review Team (DLRT), the reference dose will be updated to the highest planned dose level.

The operating characteristics of the 2-parameter BLRM design were evaluated via simulation. The cohort size was fixed to 2 or 4 subjects. All simulated studies start with the multiple subject cohorts. The initial multiple subject dose level is [redacted] μg and subsequent doses were selected based on the following rules:

- After each cohort, the next dose is the one with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive or unacceptable TPI.
- Skipping dose levels is not allowed.

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

- There have been at least 6 subjects treated at the dose recommended by the model.
- A maximum number of 36 subjects in the multiple subject cohorts is evaluated (note: this assumes that n = 4 subjects treated in single subject cohorts).

Operating characteristics are described below.

Operating characteristics

A total of [redacted] dose levels (unit: μg) were considered: [redacted] and [redacted] in these simulations of the multiple subject cohorts.

The design was evaluated for 3 possible dose-response scenarios: "Low," "Mid," and "High" MTD. Table 30 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 31 reports the operating characteristics from 10 000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33). The rate of MTD selected and the number of subjects assigned to each dose level are presented in Table 32.

[redacted]

Table 31. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33)

MTD Scenario	High		Mid		Low	
	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort	4 subjects per cohort	2 subjects per cohort
Number of Subjects	24	14	20	14	16	10
Median (IQR)	(20 to 32)	(12 to 16)	(16 to 28)	(8 to 16)	(8 to 20)	(6 to 16)
Number of DLTs	3	2	4	2	6	4
Median (IQR)	(2 to 5)	(1 to 3)	(3 to 5)	(1 to 3)	(5 to 7)	(3 to 5)
Proportion of DLT (%)	14	14	20	21	40	42
Median (IQR)	(10 to 19)	(7 to 21)	(16 to 25)	(17 to 40)	(31 to 50)	(30 to 50)
Percentage of studies recommending dose with DLT probability of:						
≤ 10%	3.3%	24.7%	2.8%	13.8%	0.9%	9.0%
> 10% and ≤ 20%	31.8%	42.0%	26.7%	37.5%	25.0%	35.7%
> 20% and ≤ 33%	64.9%	33.3%	70.5%	48.7%	74.1%	55.3%
> 33%	0%	0%	0%	0%	0%	0%
Probability of identifying MTD to have 15% to 33% DLT probability	86.7%	60.6%	88.8%	76.1%	94.6%	82.7%

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

Extremely Toxic Case

In addition, the performance of BLRM under the extremely toxic scenario was evaluated through simulations, where the DLT rate is expected to be high (the DLT rate exceeds 0.33 at all the tested dose levels) as shown in Table 33. In this extremely toxic scenario, it is highly likely to have a Grade ≥ 2 treatment-related adverse event or DLT observed at the initial dose levels. Therefore, simulation results are presented in Table 34 and Table 35 by the dose level for initiation of the multiple subject cohorts.

Operating Characteristics for Standard 3+3 Design

As a comparison, the operating characteristics from 10 000 simulated studies estimating the MTD when using a standard 3+3 design are reported in Table 36.

Table 36. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using a 3+3 Design

MTD Scenario	High	Mid	Low	Extreme
Number of Subjects Median (IQR)	14 (7 to 19)	15 (12 to 20)	14 (10 to 19)	12 (6 to 17)
Number of DLTs Median (IQR)	3 (0 to 4)	3 (2 to 5)	4 (3 o 6)	4 (3 to 6)
Proportion of DLT (%) Median (IQR)	17 (0 to 21)	23 (18 to 29)	30 (23 to 35)	36 (30 to 50)
Percentage of studies recommending dose with DLT probability of:				
≤ 10%	37.4%	39.8%	37.0%	23.7%
> 10% and ≤ 20%	62.6%	60.2%	63.0%	76.3%
> 20% and ≤ 33%	0%	0%	0%	0%
> 33%	0%	0%	0%	0%
Probability of identifying MTD to have 15% to 33% DLT probability	28.7%	18.4%	12.3%	14.3%

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose

Summary

The simulation results are summarized in Table 31 and Table 36. By comparing results in Table 31 and Table 36, we can see that while having a similar performance in controlling the number of DLTs in the trial, the 2-parameter BLRM design with the target TPI of (0.20, 0.33) has a similar or better performance in selecting the MTD, compared with the 3+3 design in the 3 scenarios.

Appendix I. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an FDA IND safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 9.

Anticipated Serious Adverse Events for Study 20170528

Cancer Pain
Metastasis
Acute Myeloid Leukaemia

[1] MedDRA Version 24.0

Amendment 7

Protocol Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia

Amgen Protocol Number (AMG 427) 20170528

IND number BB-IND 138440

NCT Number: NCT03541369

Eudra CT: 2018-001389-40

Amendment Date: 16 March 2022

Rationale:

This protocol is being amended to include additional risk mitigation measures for cytokine release syndrome (CRS). Changes related to enhanced CRS risk mitigation were mandated by the United States Food and Drug Administration (FDA) in a Partial Clinical Hold letter dated 19 July 2021 that resulted from the observation of a fatal event of grade 5 CRS observed in the study. Additionally, changes to the protocol include those requested by FDA and agreed upon by Amgen during the 30-day review period of Amgen's Complete Response submission dated 12 October 2021 (SN 0045).

The following changes were made to the protocol:

- Changes in risk mitigation measures by CRS grades to enhance patient monitoring
- Updated dose modification criteria to adapt the dosing strategy when events of CRS occur
- Changed the safety stopping rule during expansion based on grade 4 and above adverse events to a stopping rule based on dose-limiting toxicity (DLT) rate, to allow safety stopping due to grade 2 and 3 CRS events which qualify as DLT and to prevent excess stopping due to non-treatment related grade 4 events
- Additional pharmacologic interventions were added to the protocol to ensure prompt treatment of CRS when it does occur
- Adjustment of dosing strategy upon study restart (eIV infusion and lowered target doses)

- Added exclusion criterion and table related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Revised tables and language to reflect update to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading criteria for CRS and immune-effector associated neurotoxicity syndrome (ICANS)
- Added language in other protocol required therapies to include methylprednisone, siltuximab, and anakinra, and updated dose modification criteria regarding treatment interruption and re-start in case of adverse events during the infusion treatment interruption and re-start in case of adverse events during the infusion
- Added stopping rule for siltuximab dosing
- Globally, removed subcutaneous AMG 427 dosing cohorts from the study

Amendment 6

Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia

AMG 427

Amgen Protocol Number 20170528

IND number BB-IND 138440

Amendment Date: 24 March 2021

Rationale:

This protocol is being amended to allow for the enrollment of acute myeloid AML subjects with minimal/measurable residual disease (MRD).

The following changes were made to the original protocol, dated 22 March 2018:

- References to “Relapsed/Refractory” in the protocol title and in relevant sections of the protocol were removed to indicate that subjects with relapsed/refractory AML as well as subjects with MRD-positive AML will be evaluated in this trial
- Statistical considerations updated to account for MRD-positive AML subjects
- Schedule of assessments updated to include Day 8 assessments for Schedule C
- Schedule of assessments updated to include bone marrow assessments at safety follow-up and long-term follow-up visits where applicable
- Addition of extended intravenous (IV) and subcutaneous injection cohorts, using dose level review meeting (DLRM) approved doses
- Safety reporting language updated for adherence to current Amgen standard operating procedures (SOPs)
- References to Investigational Product Instruction Manual removed for adherence to current Amgen SOPs
- Update to References section
- Minor corrections and clarifications throughout

Amendment # 5

Protocol Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number AMG 427 20170528

IND number BB-IND 138440

NCT Number: NCT03541369

Eudra CT: 2018-001389-40

Amendment Date: 17 September 2020

Rationale:

The following changes were incorporated into the study:

- Addition of dose escalation cohorts, increasing the escalation sample size to n = 90 (previously n = 65).
- To provide clarification for Intra-subject dose escalation (ISDE), Etanercept (Enbrel) Vials and Etanercept (Enbrel) Substudy.
- Updates on safety risk language to align with the Informed Consent Form (ICF) and Investigator's Brochure (IB) v2.
- Administrative, editorial updates, clarifications, and typographical corrections.

As of 13 August 2020, a total of 29 subjects were enrolled and had received at least 1 dose of AMG 427 in the ongoing first-in human (FIH) study. Subjects were evaluated across [redacted] cohorts per Schedule A and Schedule C: [redacted]

The study is currently enrolling [redacted]

Preliminary clinical data from the FIH trial shows an acceptable safety profile up to doses of [redacted] ug. The ongoing FIH dose escalation has seen a total of 1 dose limiting toxicity (DLT), which occurred after a subject was dosed with [redacted] ug of AMG 427 on day 1 (resulting from cytokine release syndrome [CRS] grade 3 [liver alanine aminotransferase (ALT) grade 4 by Common Terminology for Adverse Events (CTCAE) scale, that did not

resolve to grade 1 or less in 7 days]). Low-grade CRS represents the most commonly occurring treatment-related adverse event, with CRS grade 2 seen in approximately 50% to 75% of subjects at the most recent dose cohorts. Other reported treatment-related adverse events include isolated lab abnormalities including mild hypofibrinogenemia & thrombocytopenia, and mild increases in lipase and bilirubin.

The FIH trial has seen one subject experience a morphologic leukemia free state (MLFS) at the most recent dose cohort of [redacted] μg, however no CR/CRi's have been achieved. Several more subjects throughout dose escalation have experienced transient decreases in peripheral blasts, but these did not translate to clinically meaningful responses.

Preliminary pharmacokinetic (PK) analysis from the ongoing FIH study suggests dose-related increases in free AMG 427 maximum observed concentration (Cmax) and area under the concentration-time curve (AUC). Preliminary geometric mean terminal half-life estimates range from 0.6 to 2.1 days over the evaluated range of doses up to [redacted] ug/day. Higher doses and exposures may be needed to provide thorough coverage of predicted minimally efficacious exposures estimated from in vitro AMG 427-mediated cell cytotoxicity in FLT3-expressing AML cell lines.

The emerging clinical safety and PK data from the ongoing FIH study support the exploration of additional dose levels ([redacted] ug) in the dose escalation part of the study to determine the MTD for AMG 427. Recommendations to explore additional dose levels will be made by the Dose Level Review Team (DLRT) following review of the PK, safety, and efficacy data for each enrolled cohort.

Amendment 4

Protocol Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number (AMG 427) 20170528

Amendment Date: 17 February 2020

Rationale:

The protocol is being amended according to guidance provided by Food and Drug Administration (FDA).

Amendment 3

Protocol Title: A Phase 1 First-in-human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

Amgen Protocol Number: AMG 427 20170528

Amendment Date: 26 November 2019

Rationale:

The following updates were made to the protocol, dated 08 June 2018:

- New dosing schedule with an additional Day 3 infusion to current dosing regimen. Addition made based on pharmacological data, in order to provide sustained exposure of AMG 427 above the predicted minimally efficacious exposure for the entire treatment cycle.
- Schedule of assessments updated to include bone marrow assessments at safety follow-up and long-term follow-up visits where applicable
- Disease-related events and all associated references were removed for the purpose of adherence to current Amgen SOPs
- Reference to self-evident corrections (SEC) were removed for the purpose of adherence to current Amgen SOPs
- Update to References section
- Minor corrections and clarifications throughout
- Addition of Substudy adding Enbrel (etanercept) as pre-medication, in order to explore better safety, tolerability, and efficacy of BiTE therapy.

Amendment 2

Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Acute Myeloid Leukemia

AMG 427
Amgen Protocol Number 20170528
IND number BB-IND 138440

Amendment Date: 30-April-2019

Rationale:

This protocol is being amended to allow for the enrollment of AML subjects with measurable/minimal residual disease (MRD).

The following changes were made to the original protocol, dated 08 June 2018:

- References to “Relapsed/Refractory” in the protocol title and in relevant sections of the protocol were removed to indicate that subjects with relapsed/refractory AML as well as subjects with measurable/minimal residual disease (MRD)-positive AML will be evaluated in this trial
- Statistical considerations updated to account for MRD-positive AML subjects
- Schedule of assessments updated to include bone marrow assessments at safety follow-up and long-term follow-up visits where applicable
- Disease-related events and all associated references were removed for the purpose of adherence to current Amgen SOPs
- Reference to self-evident corrections (SEC) were removed for the purpose of adherence to current Amgen SOPs
- Update to References section
- Minor corrections and clarifications throughout

Amendment 1

Title: A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 427 in Subjects With Relapsed/Refractory Acute Myeloid Leukemia

AMG 427
Amgen Protocol Number 20170528
IND number BB-IND 138440

Amendment Date: 08 June 2018

Rationale: This protocol is being amended based on comments received from the FDA upon submission of the US IND on April 9, 2018. All updates are in line with changes requested by the agency.

The following changes were made to the original protocol, dated 22 March 2018:

- Eligibility criteria was revised to include patients who have failed treatment with, are intolerant to, or are not candidates for available therapies for treatment of relapsed or refractory AML
- Dose Limiting Toxicity (DLT) window will start on D1 (start of the administration of the first infusion) and last for 28 days for all cohorts.
- Confirmed Hy's Law cases will be included as DLTs.
- Subjects experiencing a Grade 4 adverse event during infusion will be permanently discontinued from investigational product
- Dosing instructions for tocilizumab are updated such that subjects can be given up to 3 additional doses of tocilizumab, 8 hours apart, if needed.
- Cohort size in dose expansion is modified to n=6
- Early stopping rules and efficacy futility rules have been implemented in dose expansion phase based on DLT criteria; enrollment to dose expansion will be paused or possibly terminated if these rules are met. Secondary endpoint (efficacy parameters) has been updated to reflect the efficacy futility rules.
- Adverse events will be recorded starting from the time of consent, rather than from the time of dosing. Schedule of events was updated to reflect this change.
- Statement added to indicate that FDA will be provided with brief interim results of the dose escalation phase once MTD and RP2D is established.
- Clarifications/minor corrections to Schedule of Assessments