Statistical Analysis Plan

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
Short Protocol Title:	FIH study to evaluate safety, tolerability, PK, PD & Efficacy of AMG 427
Protocol Number:	20170528
NCT Number:	NCT03541369
Authors:	[redacted], Global Biostatistical Science [redacted] **Global Biostatistical Science** [redacted] Global Biostatistical Science
Sponsor:	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 Phone: +1 805 447 1000
SAP Date:	**Document Version** — **Date** **Amendment 2 (v3.0)** — **25 April 2022** Amendment 1 (v2.0) — 07 Dec 2020 Original (v1.0) — 22 Oct 2018

Version Number	**Date (DDMMMYYYY)**	**Summary of Changes, including rationale for changes**
Original (v1.0)	22OCT2018	NA
Amendment 1 (v2.0)	07Dec2020	• Add the design and analysis for Schedule B • Update the endpoints, planned doses, sample size to be consistent with protocol • Make a few clarifications on definition and analysis methods • Other administrative changes
Amendment 2 (v3.0)	**25Apr2022**	• **Updated the study design for MRD+ AML and eIV groups according to protocol** • **Updated the sample size section** • **Added the definition and analysis for MRD+ AML and eIV groups** • **Added database disposition for each planned analysis** • **Updated the imputation rules as per new DES SAP template** • **Removed the QTcF threshold definitions.**

Table of Contents

List of Tables

List of Figures

[redacted]

List of Abbreviations

Abbreviation	Explanation
AML	Acute Myeloid Leukemia
AUC	Area under concentration time curve
C_{max}	maximum observed concentration
CRF	case report form
CRS	Cytokine Release Syndrome
DLRM	dose level review meeting
DLT	dose limiting toxicity
ECG	Electrocardiogram
eCRF	electronic case report form
end of study for individual subject	defined as the last date that protocol-specified procedures are conducted for an individual subject
end of treatment	defined as the date of final assessment for the protocol specified treatment phase of the study for an individual subject
end of study (primary completion)	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).
FIH	First in Human
Ig	Immunoglobulin
ICF	informed consent form
IP	Investigational Product
MRD	**Minimal/measurable Residual Disease**
NA	**Not Applicable**
PD	Pharmacodynamic
PK	Pharmacokinetic
PR	the interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram
QRS	the interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; represents the time it takes for depolarization of the ventricles
QT	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 electrocardiogram
QTc	QT interval corrected for heart rate using accepted methodology
RFS	Relapse Free Survival
R/R	Relapsed/Refractory

study day 1	defined as the first day that protocol specified investigational product is administered to the subject
t_{max}	time to maximum concentration

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **7** for study 20170528, AMG 427 dated **16 March 2022**. The scope of this plan includes the interim analysis, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. PK, PD/biomarker analyses will be provided by Clinical Pharmacology, Modeling and Simulation (CPMS) group and clinical biomarker group in Department of Translational Medicine, respectively. Separate SSAP will be created to prespecify additional analysis required to support assessment of an alternative for prophylaxis of cytokine release syndrome (CRS), the main on-target toxicity identified for AMG 427, in schedule B, in subjects with R/R AML.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• 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**	• Safety: Dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs)

Secondary	
• Characterize the pharmacokinetics (PK) of AMG 427	• 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
• Evaluate the anti-leukemia activity 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
[redacted]

2.2 Hypotheses and/or Estimations

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. Study Overview

3.1 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 US, Australia, Canada, Japan, South Korea, and Germany. Additional countries or sites may be added if necessary.

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.

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 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 an additional **doses** on D3 **and D8**, to comprise a 2-week cycle with doses on D1/D3/D5/**D8**. 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+ cohorts**) will be enrolled in a dose expansion cohort to gain further clinical experience, safety, and efficacy data in subjects administered AMG 427.

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.**

The study will have three alternative dosing schedules:

- Schedule A: **- CLOSED**
  - D1/D5 or D1/D5/D12/D19 (dexamethasone prophylaxis)
- Schedule B**: Etanercept Substudy (R/R AML) - CLOSED**
  - D1/D5 or D1/D5/D12/D19 (etanercept 2 days prior to each cycle) Etanercept (Enbrel) 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: **(Protocol Table 16 through Table 21) FIH, eIV (R/R AML), and 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 (from protocol) for additional whole blood MRD collection, or Table 23 (from protocol), as applicable.**

After reviewing additional PK, safety, and efficacy data, the DLRT may recommend the administration of additional **doses** on day 12 and day 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), and 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**/injection** related reaction at the first dose (see example in Figure 1). Dose steps may occur at the D3, D5, **D8**, D12 or D19 infusions. 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. Cycle 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 and 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 1. For logistical reasons, there is a ± 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 determined 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

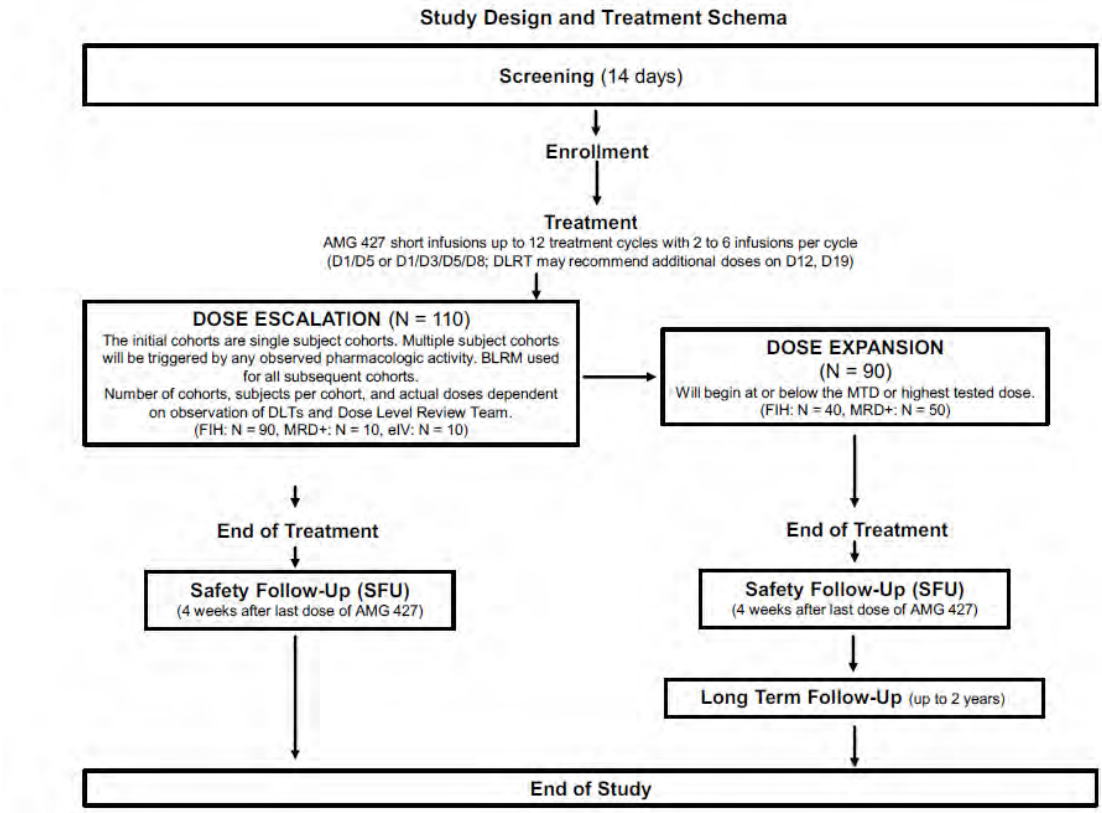
dose step may also be implemented in a cycle if this was considered appropriate and necessary to allow further dose escalation. This second dose step would be performed the same way as described above. In this case, a third MTD would be estimated for the dose to be administered after the second dose 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. 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.

Study Design and Treatment Schema



3.2 Sample Size

It is anticipated that approximately **200** subjects will be enrolled in this study, **with** approximately **110** subjects enrolled in the dose escalation cohorts and **90** subjects in the dose expansion cohort:

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 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 a 40% response rate, the expected 80% CI would be 30.6% and 50.1%.**

3.3 Adaptive Design

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK and PD of AMG 427 in subjects with MRD+ or R/R AML using a Bayesian logistic regression model (BLRM: Neuenschwander et al, 2008). See Protocol Appendix H for the description of the two-parameter BLRM 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** event rate is greater than 2**0**% is > 80%. The stopping boundaries assuming a prior distribution of Beta (0.40, 1.60) are presented in Table 1

and the operating characteristics with pre-specified batch size of 6 new subjects per batch are presented in Table 2. The evaluations could occur more frequently if necessary to address emerging safety concerns.

Table 1. Stopping Boundary for Dose Expansion With Posterior Probability of 80% DLT Limit of 20%

Number of subjects	Pause study enrolment 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 2. 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 3 shows the probability of early stopping and the average sample size in dose expansion

Table 3. Probability of Early Stopping and the Average Sample Size in R/R AML 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 4 shows the probability of early stopping and the average sample size in dose expansion.

Table 4. Probability of Early Stopping and the Average Sample Size in MRD+ AML 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	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 adhoc DLRM coincide with regular DLRM, they may be combined.

Number of Subjects Treated with Siltuximab	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
	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.

4. Covariates and Subgroups

4.1 Planned Covariates

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

4.2 Subgroups

[redacted]

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

5. Definitions

Age at Enrollment

Subject age at enrollment will be collected using the age in years in the clinical database.

$AUC_{0\text{-last}}$

Area under the concentration-time curve from time 0 (time of investigational product administration) to the time of the last quantifiable concentration.

Baseline

Except ECG for any variable, unless otherwise defined, baseline is the last assessment taken prior to the first investigational product administration.

ECG analysis value

The mean value of triplicate will be calculated and used in the analysis. If an ECG is missing within a triplicate, all available data will be averaged for that time point. Further, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate at a time point will be included in the mean for that time point.

Baseline ECG

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])

The mean of the values within a triplicate should be calculated before taking the mean of the triplicate averages. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Percent Change from Baseline

Percent change from Baseline is the arithmetic difference between post-Baseline and Baseline divided by Baseline values times 100.

Percent change from baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Fold change from Baseline

Fold change from Baseline equals the post-Baseline value divide by the Baseline value.

Fold change from baseline = Post-baseline Value / Baseline Value

C_{max}

Maximum observed serum concentration.

C_{min}

Minimum observed serum concentration

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. 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.

End of Study:

End of study is 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.

Enrollment Date

Enrollment date is defined as the date when the investigator confirms that the subject has met all eligibility criteria and will be collected on the enrollment eCRF.

Change from Baseline

Change from Baseline is the arithmetic difference between post-Baseline and Baseline.

Change (absolute) from Baseline= (Post-baseline Value – Baseline Value)

Study Day

Post study day 1: study day= (date - date of Study Day 1) + 1

Pre study day 1: study day= (date – date of Study Day 1)

Study Day 1

Study day 1 is defined as the first day of administration of the investigational product after enrollment. The day prior to Study Day 1 is considered Day -1.

Investigational Product

The term 'investigational product' is used in reference to AMG 427.

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events are events categorized as Adverse Events (AEs) starting on or after the first dose of investigational product (AMG 427), as determined by the flag indicating if the adverse event started prior to the first dose (AMG 427) on the Events CRF and up to and including 30 days after the end of investigational product (AMG 427) or the end of study (EOS) date, whichever is earlier.

Treatment-Related AE

A treatment-related AE is any treatment-emergent adverse event that per investigator review has a reasonable possibility of being caused by the investigational product. **Event with missing/unknown relationship to treatment will be assumed to be treatment-related.**

Dose Limiting Toxicities (DLT)

A DLT will be defined as any of the events described **in protocol section 6.2.1.3** 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 decision by the DLRT after review of the adverse event and all available safety data. Investigators will determine whether an adverse event qualifies as a DLT per protocol Section 6.2.1.3 and it will be collected by the flag indicating DLT in Events CRF.

Maximum Tolerated Dose (MTD)

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.

Overall Response (for R/R AML)

Overall response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi), morphologic leukemia-free state, partial remission (all according to Revised International Working Group [IWG] response criteria) or CR with partial hematologic recovery (CRh).

Duration of Response (DOR) (for R/R AML)

Duration of response is defined as the number of days between the date of the first disease assessment indicating an overall response through the subsequent date of progression or relapse as defined by revised IWG response criteria or death due to any cause, or where applicable date of censoring [date of first progressive disease assessment or relapse or death or date of censoring – date of the first objective response result +1]. Subjects who respond and have not progressed or relapse or died while on study will be censored at the last adequate disease assessment date. Subjects who do not achieve an overall response will be excluded from the analysis of duration of response.

MRD Conversion Rate

MRD conversion rate is the number of subject achieve MRD- among subjects at who are MRD+ at enrollment. [redacted]

Overall Survival

Overall survival (OS) is defined as the time from the start of treatment (Study day 1) until event of death due to any cause.

OS time (Days) = Date of death – Study Day 1 + 1

OS time (Months) = (Date of death – Study Day 1 + 1)/30.4

Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (ie, the data cutoff date), the subject will be censored at the analysis trigger date.

Relapse-free Survival (RFS) (for MRD+ group)

RFS time will be calculated from the date of first administration of AMG 427 until the date of a hematologic relapse or death, whichever occurs first. Subjects still alive and relapse-free will be censored on their last disease assessment date.

6. Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

6.1 Full Analysis Set

NA

6.2 Safety Analysis Set

All subjects that are enrolled and received at least 1 dose of AMG 427.

6.3 Per Protocol Set(s)

NA

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

NA

6.5 Pharmacokinetic/Pharmacodynamic Analyses Set(s)

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.

6.6 Interim Analyses Set(s)

NA

6.7 Study-specific Analysis Sets

Dose Limiting Toxicity (DLT) Evaluable Analysis Set:

DLT Evaluable Analysis Set includes all DLT-evaluable subjects defined as all subjects who have received the doses planned for the respective cohort, and completed the DLT window of 28 days for all cohorts unless 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. The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent. The analysis of DLT will be restricted to DLT Evaluable Analysis Set.

7. Planned Analyses

The following data analyses are planned:

(1) 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.

(2) Final analysis after all 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.

7.1 Interim Analysis 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 one-parameter Continual Reassessment Method (CRM) model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

Ad-hoc interim analysis for efficacy parameters will be conducted after dose escalation is completed. Once preliminary MTD and RP2D are established, FDA will be provided with brief interim results of the dose escalation phase.

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 decisions: 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 ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. Modeling of

available potential safety risk data (eg, for thrombocytopenia) to predict safety risk for dose escalation decisions may also be considered.

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 decisions 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 day
- 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 Dose Level Review Meetings (DLRMs). Subjects' cytogenetic profiles (eg, potentially higher cytokine release in monocytic AML) should be taken into consideration for DLRT decisions.

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.

DLRM analysis is based on as-is snapshot including all data up to the data cutoff.

7.2 Primary Analysis

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

Primary analysis is based on locked database.

7.3 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. **Final analysis is based on final locked database to prevent future change.**

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

The following imputation for missing or incomplete data will be performed if required: Incomplete adverse event and concomitant medication dates missing data will be imputed as described in Appendix G.

- Non-pharmacokinetic measurements (eg. biomarker data) that are below the lower limit of quantification will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.
- Laboratory measurements that are below the quantification limits will be considered equal to the lower limit of quantification for all analyses unless explicitly noted otherwise.
- PK concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PK parameters

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations in each cohort. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Pharmacokinetic (PK) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 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 two-parameter BLRM will be used to estimate the dose-toxicity relationship. Separate BLRM analysis will be conducted for each dose regimen, eg, MTD1 and MTD2 if there is one dose step.

A two-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 one 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 pi is approximately 0.05 for the [redacted] µg dose and 0.25 for the reference dose. Once the [redacted] ug is deemed safe by Dose Level Review Team (DLRT), the reference dose will be updated to the highest planned dose level. **For more details of BLRM, please refer the Appendix H in the protocol.**

9.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, received at least one dose of AMG 427, completed investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, discontinued the study (including reasons for discontinuing) will be summarized overall and by dose cohort. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented. A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting, reason for discontinuation of treatment, and reason for discontinuing the study will be provided.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. **The final IPD list is used to produce the summary of IPDs table and the list of subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.**

9.4 Demographic and Baseline Characteristics

Demographic (i.e., age, age groups [18-64, 65-74, 75-84 and >= 85], sex, race, ethnicity) and baseline characteristics will be summarized by dose cohort and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple-race as well as by the combination of race.

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

NA

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

For R/R AML, the proportion of subjects with an overall response 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**/RP2D**. DOR will be analyzed using Kaplan-Meier method. Kaplan-Meier curves and estimates for rates and 80% CI at selected time points will be presented **for subjects in dose-expansion cohort**. Only subjects with an overall response will be analyzed for DOR.

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/RP2D. Relapse free survival and overall survival will be analyzed using Kaplan-Meier method. Kaplan-Meier curves and estimates for rates and 80% CI at selected time points will be presented for subjects in dose-expansion cohort.

[redacted] will be considered exploratory.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Subject incidence of DLTs will be used to fit the BLRM model to estimate the probability of having a DLT across dose levels at DLRM. Separate BLRM analysis will be conducted for each dose regimen, eg, MTD1 and MTD2 if there is one dose step. The BLRM analysis will be performed based on the Section 9.1 in Statistical Analysis Plan. Summary of the subject incidence of DLT will be provided.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version [2**4**.0] or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using CTCAE version 4.0 or later. For Cytokine release syndrome (CRS) events, grading is based on Lee et al,

2014 for Cohort [redacted] and Etanercept substudy in FIH group; and is based on Lee et al, 2019 for Cohort [redacted] onwards in FIH group, eIV group and MRD+ group, per protocol. 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.

The subject incidence of adverse events will be summarized for all **treatment-emergent adverse events (TEAE)**, treatment-related adverse events, serious adverse events (SAEs), grade 3 and above adverse events, adverse events leading to withdrawal of investigational product, adverse events leading to interruption of investigational product and fatal adverse events by system organ class, preferred term, and worst **severity** grade. Also, all TEAEs, **treatment-related adverse events,** SAEs and grade 3 and above adverse events will be summarized by preferred term only in descending order of frequency.

Treatment-emergent events of interest (EOIs) will be summarized by EOI category and preferred term. In addition, for each EOI category, the subject incidence of all, serious, grade 3 and above, fatal, leading to withdrawal of investigational product, leading to interruption of investigational product will be summarized.

The safety analysis will be provided for FIH, eIV and MRD+ groups separately.

9.6.3 Laboratory Test Results

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

Summaries of the absolute value and/or changes from baseline at each scheduled assessment may be provided for selected laboratory parameters of interest.

Shifts tables indicating the change between the baseline and the maximum post dose CTCAE grades (CTCAE version 4.0 or later) for an increased value, and the maximum post dose grade for a decreased value will be provided for selected laboratory parameters of interest.

9.6.4 Vital Signs

Vital signs data will be listed and reviewed for each subject in DLRM. 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.

9.6.5 Physical Measurements

NA

9.6.6 Electrocardiogram

All on-study electrocardiogram (ECG) data will be listed and selected parameters of interest may be presented using mean plots.

Summaries over time and/or changes from baseline over time will be provided for PR, QRS, QT, QTc, RR.

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The number of cycles **started**, number of doses of investigational product, **cumulative dose**, **cumulative dose per cycle**, the total dose and duration of exposure will be summarized.

Details for each AMG 427 administration will be listed for every subject. In addition, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.9 Exposure to Non-investigational Product

NA

9.6.10 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to dexamethasone. The number of doses of dexamethasone and the total dose in mg will be summarized.

9.6.11 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medication will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

Analysis for the Enbrel substudy will be described in Supplemental Statistical analysis plan (SSAP).

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Serum concentrations of AMG 427 will be determined using a validated assay.

PK parameters will include, but are not limited to half-life ($t_{1/2}$; if feasible), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}) and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$). Pharmacokinetic parameters will be estimated using standard non-compartmental approaches and summarized by dose level using means, standard deviations, medians, minimums, and maximums.

Serum concentrations below the lower limit of quantifications will be set to zero for the estimation of the pharmacokinetic parameters for each subject and for the calculation of the summary statistic for each time point. Actual dosing and sampling time will be used for all calculations. The reasons for excluding any sample from the analyses will be provided.

Individual concentration-time data will be summarized by dose level. Individual concentration-time data will also be tabulated and presented graphically. Summary statistics will be computed for each sampling time and parameter as appropriate.

Additional PK analyses, including but not limited to analysis of the relationship between AMG 427 dose and exposure parameters (AUC and C_{max}) and dose proportionality assessments, may also be conducted. 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.

9.7.2 Analyses of Clinical Outcome Assessments

NA

9.7.3 Analyses of Health Economic Endpoints

NA

9.7.4 Analyses of Biomarker Endpoints

Analyses of biomarker endpoints will be performed by Clinical Biomarker and Diagnostics (CBD) function and details will be captured in a separate data analysis plan.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Babb J, Rogatko A, Zacks S. Cancer Phase I Clinical Trias: Efficient Dose Escalation with Overdose Control. *Statistics in Medicine* 1998;17:1103-1120.

Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21(24):4642-9.

Clopper CJ, Person ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometricka* 1934;26:404-13.

Lee DW, Gardner R, Porter DL, et al.: Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124(2):188-195.

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

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.

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

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, Maus MV, Park JH, Mead E, Pavletic S, Go WY, Eldjerou L, Gardner RA, Frey N, Curran KJ, Peggs K, Pasquini M, DiPersio JF, van den Brink MRM, Komanduri KV, Grupp SA, Neelapu SS. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638. doi: 10.1016/j.bbmt.2018.12.758. Epub 2018 Dec 25. PMID: 30592986.

12. Prioritization of Analyses

NA

13. Data Not Covered by This Plan

NA

14. Appendices

Appendix A. Reference Values/Toxicity Grades

NA

Appendix B. Concomitant Medications

NA

Appendix C. Clinical Outcome Assessment Forms/Instruments

NA

Appendix D. Health Economic Forms/Instruments

NA

Appendix E. Details of PK or PK/PD Methods for Modeling

NA

Appendix F. Analytical Windows

NA

Appendix G. Handling of Dates, Incomplete Dates and Missing Dates

Below imputation rules will be used to impute start date and stop date of AE and Concomitant medication. Date of prior anti-cancer therapy, PD-1, PD-L1 and metastasis will be imputed using the same rule when only the date is missing (no imputation when month or year is missing).

Imputation Rules for Partial or Missing Start Dates

The reference date for the following rules is the date of first dose[of study drug].

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1=Impute the date of first dose; 2=Impute the first of the month; 3=Impute January 1 of the year; 4=Impute January 1 of the stop year
Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month or first day of year if month is also missing.

Imputation Rules for Partial or Missing Stop Dates

Initial imputation

- **If the month and year are present, impute the last day of that month.**
- **If only the year is present, impute December 31 of that year.**
- **If the stop date is entirely missing, assume the event or medication is ongoing.**

If the imputed stop date is before the start date, set stop date to missing.

If the imputed stop date is after the death date, impute as death date.

Imputation Rules for Partial or Missing Death Dates

If death year and month are available but day is missing:

- **If yyyymm for the date last known to be alive equals yyyymm for death date, set death date to the day after the date last known to be alive.**
- **If yyyymm for the date last known to be alive is less than the yyyymm for death date, set death date to the first day of the death month.**
- **[If yyyymm for the date last known to be alive is greater than yyyymm for death date, assume date last known to be alive is in error, set death date to the first day of the death month.**

If month and day are missing and year of death is known:

- **If yyyy for the date last known to be alive equals yyyy for death date, set death date to the day after last known to be alive date.**
- **If yyyy for the date last known to be alive is less than yyyy for death date, set death date to the first day of the death year.**
- **If yyyy for the date last known to be alive is greater than yyyy for death date, assume date last known to be alive is in error, set death date to the first day of the death year.**

If a death date is totally missing:

Do not impute and censor the subject survival time.