Statistical Analysis Plan

Protocol Title:	A Phase 1 First-In-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 673 Administered as Short Term Intravenous Infusions in Subjects With Relapsed/Refractory Acute Myeloid Leukemia
Short Protocol Title:	FIH study to evaluate safety, tolerability, PK, PD & Efficacy of AMG 673
Protocol Number:	20160377
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	25AUG2017	Original
Amendment 1 (v2.0)	04APR2022	• Updated the SAP as per Protocol Amendment 5. Changed the amendment date from 24 June 2019 to **11 December 2019** throughout the document. • Clarification of some definitions, such as treatment-emergent adverse event (TEAE), overall response, duration of response (DOR), time to response (TTR), time to progression(event-free survival (EFS)). • Detailed Summary of changes provided in the Appendix C

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List of Abbreviations

Abbreviation	Explanation
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).
Ig	Immunoglobulin
ICF	informed consent form
IP	Investigational Product
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
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 for study **20160377**, **AMG 673** dated **11 December 2019**. 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.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 673 in adult subjects with relapsed/refractory AML • Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)]	• Safety: subject incidence and grade of adverse events and dose limiting toxicities (DLTs)
Key Secondary	
• Evaluate the pharmacokinetics (PK) of AMG 673 • Evaluate the anti-leukemia activity of AMG 673 by evaluating: - the number and proportion of subjects who respond to treatment with AMG 673. Response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi) or morphologic leukemia-free state (all according to Revised International Working Group [IWG] response criteria) or CR with partial hematologic recovery (CRh*). - the duration of response, time to progression, and time to response.	• Pharmacokinetic parameters including, but not limited to: half-life, maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) and clearance of AMG 673. • Efficacy parameters: response rate (response defined as CR/CRi/morphologic leukemia-free state [per modified IWG criteria] or CRh*), duration of response, time to progression, time to response.

Exploratory

[redacted]

2.2 Hypotheses and/or Estimations

AMG 673 will demonstrate evidence of anti-leukemic activity at a well-tolerated dose in subjects with AML.

3. Study Overview

3.1 Study Design

This is a first-in-human, open-label, phase 1, sequential dose escalation study. AMG 673 will be evaluated as a short term intravenous (IV) infusion in adult subjects with relapsed/refractory AML. The study will be conducted at approximately **10** sites in Australia, Germany and the United States. Additional sites may be added later.

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and pharmacodynamics (PD) **using 2 schedules of AMG 673 administration: Schedule A**

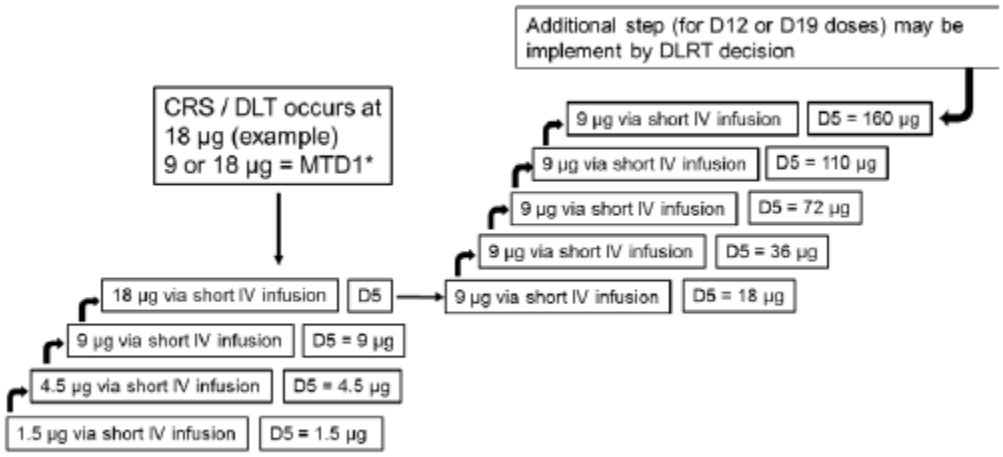
(D1/D5 dosing) and Schedule B (QD dosing for cycle 1 followed by twice weekly dosing in following cycles).

For Schedule A, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 0.05 µg, 0.15 µg, 0.45 µg, 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the first cohort will be 0.05 µg administered as short term IV infusions on D1 and D5. The doses administered for the cohorts following cohort 1 will be recommended by the Dose Level Review Team (DLRT). The DLRT may recommend on the administration of up to 2 additional infusions on D12 and D19 of a cycle for a future cohort. All subjects will be pre treated with an 8-mg dose of IV dexamethasone 1 hour prior to day 1 and day 5 AMG 673 doses and prior to each step-up dose of AMG 673**.** Each cycle will last for 14 days in the cohorts receiving only 2 doses (Day 1, 5) and 28 days in the cohorts receiving 4 doses (Day 1, 5, 12, 19). **Each** cycle will be followed by a treatment-free interval for **0 to 14 days depending on treatment response and recovery of blood counts, but may be extended as described in Section 6.2.1.1.1 in the protocol fter consultation with Sponsor.** The D5 infusion, and the D12/D19 infusions (if applicable) may be at the same dose as the preceding infusion 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. There is a ± 1 day window for dosing visits which may be implemented after consultation with Sponsor.

For Schedule B, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the cohort 1 on Schedule B will be 72 µg administered as short-term IV infusions daily (QD) during the 14-day cycle 1 after the 72 µg target dose is found to be relatively safe and tolerable by the DLRT for Schedule A. Cohort 2 and higher will include step-up doses added in each cohort administered in two day increments after the previous step dose up to the target dose in cycle 1 (eg, cohort 2 will start with 72 µg for 2 days followed by 110 µg administered on D3 to D14; cohort 3 will start with 72 µg for 2 days followed by 110 µg on D3 for 2 days followed by 150 µg on D5 to D14, etc). Cycle 2+ doses will be given on days 1, 4, 8 and 11 at the target dose. See Table 3 and Section 6.2.1.1.2 in the protocol for Schedule B dosing schema by cohort in the protocol. All subjects will be pre treated with an 8-mg dose of IV dexamethasone 1 hour

prior to the first dose on day 1 and prior to each step-up dose in cycle 1 and prior to all doses in cycle 2 and beyond. There is no treatment free interval between cycle 1 and cycle 2. Beyond cycle 2, a treatment-free interval is allowed for 0 to 14 days depending on treatment response and recovery of blood counts, and may be extended as described in Section 6.2.1.1.1 after consultation with the sponsor. Adjustments to dose level, dose frequency and a duration of step dosing may be considered after recommendation of DLRT based on review of available safety, PK, and PD data.

Figure Example of Establishing Step Dosing Once MTD1 is Established



*The MTD1 will be determined by the DLRT

Dose Escalation Cohorts

Dose Escalation will be conducted in 2 stages: a single subject stage **(Schedule A only)** and a multiple subjects stage. In the single subject cohorts, cohorts 1 and 2, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events related to AMG 673 will be observed. Multiple subject cohorts, starting with cohort 3, will enroll and the cohort size will be extended to 3-4 subjects per cohort. The Bayesian logistic regression model (BLRM) design will be used to guide dose escalation. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the dose level review team (DLRT) after considering all information. Subjects will be assessed for dose limiting toxicities (DLTs) for the duration of their **first** treatment cycle (ie, 2 weeks from D1 for subjects who receive 2 doses and 4 weeks for subjects who receive 4 **doses in Schedule A and 4 weeks from D1 for subjects in Schedule B)**. Subjects who complete the DLT period

may proceed to a higher dose level for the following treatment cycle **after** the next dose level has been deemed safe by **the DLRT, after consultation with Sponsor, if no DLT was reported for that subject** and no ≥ grade 3 adverse event(s), deemed treatment related by the investigator, are reported for that subject.

Estimation of initial and target MTDs

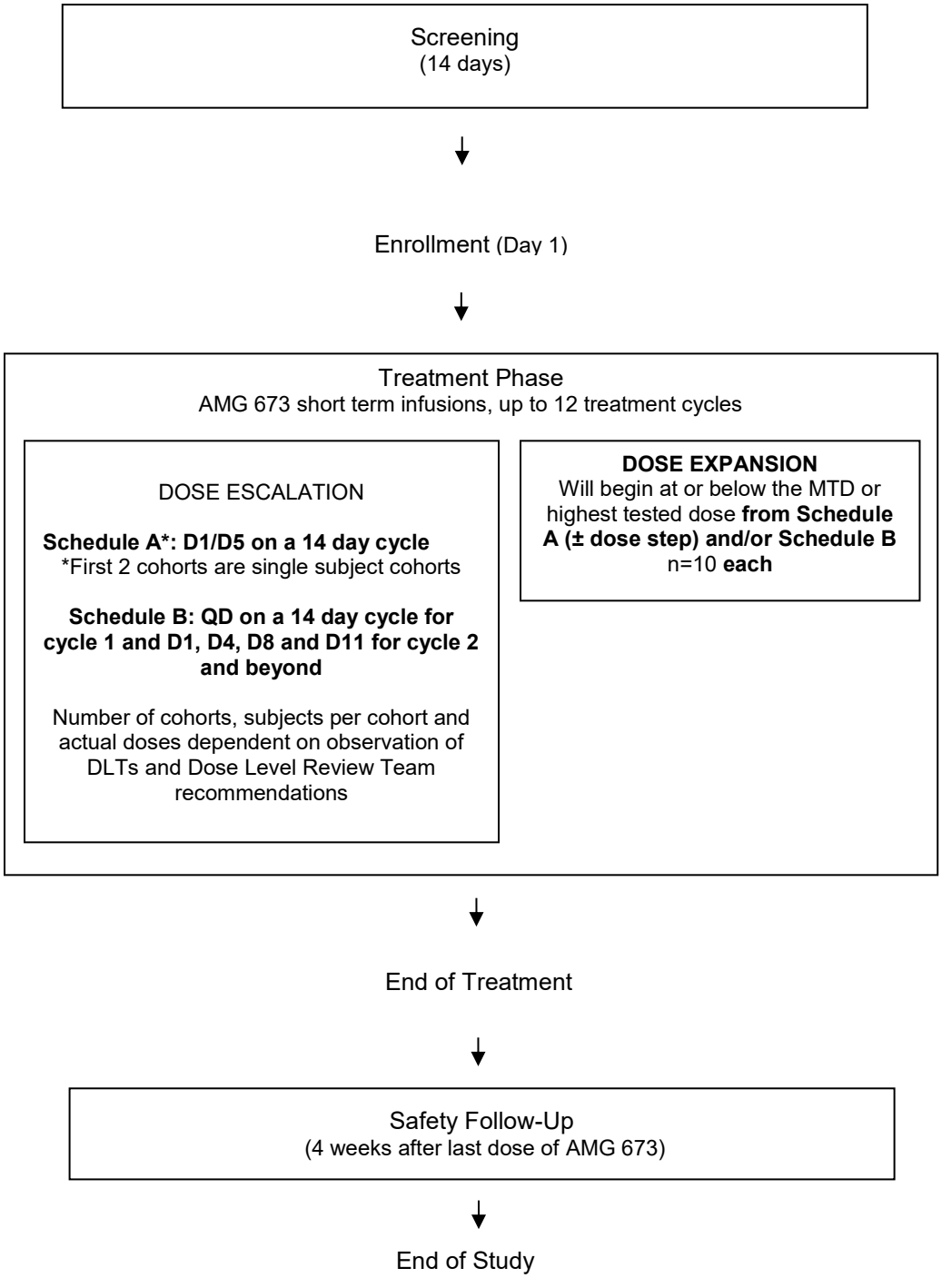
For Schedule A, it is anticipated that **at least** 2 MTDs may be estimated, one for the initial dosing and one for the subsequent **step** dosing. Should the initial dose be limited by adverse events related to first dose effects, the second MTD for the target dose will be estimated after giving the initial dose at MTD (step dose). 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.

Schedule B will be initiated after preliminary safety data of AMG 673 in Schedule A (eg, MTD1 is estimated to be ≥72 µg) become available and may be conducted in parallel with Schedule A per Sponsor's decision. The MTD for Schedule B will be estimated following the dose escalation described in Section 6.2.1.1.2 in the protocol and guided by BLRM described above.

Expansion Cohort

For each Schedule, upon completion of the dose escalation cohorts, additional subjects (up to 10) **may** be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. Additional expansion cohorts may be covered by a protocol amendment to test alternative dose levels or biologic subsets.

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 **for each schedule**


Screening
(14 days)
Enrollment (Day 1)
Treatment Phase
AMG 673 short term infusions, up to 12 treatment cycles
DOSE ESCALATION
Schedule A*: D1/D5 on a 14 day cycle
*First 2 cohorts are single subject cohorts
Schedule B: QD on a 14 day cycle for cycle 1 and D1, D4, D8 and D11 for cycle 2 and beyond
Number of cohorts, subjects per cohort and actual doses dependent on observation of DLTs and Dose Level Review Team recommendations
DOSE EXPANSION
Will begin at or below the MTD or highest tested dose from Schedule A (± dose step) and/or Schedule B
n=10 each
End of Treatment
Safety Follow-Up
(4 weeks after last dose of AMG 673)
End of Study

3.2 Sample Size

It is anticipated that approximately **95** subjects will be enrolled in this study. **For Schedule A, a**pproximately 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort. **For Schedule B, up to 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort.** For ethical and operational reasons subjects who already are in the screening phase at the time of enrollment stop (end of expansion phase) **may** 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 **or a schedule may be discontinued**.

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 3 subjects per cohort, there is a 27-70% probability of observing at least one 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 10 will provide a 65% probability of observing at least one adverse event with 10% incidence rate and 89% probability of observing at least one adverse event with 20% incidence rate. An exact 80% binomial confidence interval (CI) will be provided for overall response rate. With the 10 subjects and 20% overall response rate, the expected 80% CI would be 5.5% to 45.0% with the half-width 19.8%.

4. Covariates and Subgroups

4.1 Planned Covariates

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

[redacted]

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

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 timepoint. Further, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate at a timepoint will be included in the mean for that timepoint.

Baseline ECG

The baseline ECG is defined as the average of the mean of the triplicates at predose assessments from cycle 1 day 1; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$QTcB=QT/(RR/1000)^{1/2}$

Change From Baseline

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

C_{max}

Maximum observed serum concentration.

C_{min}

Minimum observed serum concentration

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 2 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: The end of study date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit); the final analysis will occur at this time.

Enrollment Date

Enrollment date is defined as the first dose of IP date.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

$QTcF=QT/(RR/1000)^{1/3}$

Investigational Product

The term ‘investigational product’ is used in reference to AMG 673.

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

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.

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events are events categorized as Adverse Events (AEs) **including disease related events** starting on or after the first dose of investigational product, as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to end of study (EOS).

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.

Dose Limiting Toxicities (DLT)

DLT will be determined by "Is this event a Dose Limiting Toxicity (DLT)?" equal to "Yes" on the Events eCRF. Investigators will determine whether an adverse event qualifies as a DLT per protocol Section 6.2.1.3

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

Overall response is defined as achieving any of the following response**: CR, CRh*, CRi or MLFS.**

Duration of Response (DOR)

Duration of response is defined as the interval from the date of the first disease assessment indicating an overall response to the first documented relapse or death due to any cause, whichever occurs first. Subjects without relapse or death until the analysis data cut-off date will be censored at the last adequate disease assessment date. Only subjects with a response will be evaluated for DOR.

DOR time in days = earlier of (date of first relapse or disease progression or death or date of censoring) – date of the first observation of overall response + 1.

Time to Response (TTR)

Time to response defined as the interval from the first administration of AMG 673 to the first documentation of response. Time to response is evaluated only for subjects who achieved a response.
Time to response is calculated as the number of days:
(date of first response – date of study day 1 + 1).

Time to Progression (Event-free Survival):

Event-free survival (EFS) is defined as the interval from first administration of AMG 673 to the earliest of date of treatment failure, relapse for responders, or death due to any cause. Censoring is at the last evaluable post-baseline response assessment; otherwise, at first administration of AMG673. For non-responders, the event date for treatment failure is assigned as the date of first administration of AMG 673.

Event-free Survival in days = earlier of (date of treatment failure or relapse or death or date of censoring) – date of the first administration of AMG 673 + 1.

6. Analysis Sets

6.1 Safety Analysis Set

All subjects that are enrolled and received at least 1 dose of AMG 673

6.2 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.

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 2 cycles of treatment.

(2) Final analysis after all subjects have ended the study

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 enrolment and dosing decisions.

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

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. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: early development leader**/Medical Monitor and** global safety officer, or their approved designees, clinical study manager, **and** biostatistician **and** PK scientist (optional). Other functional area representatives **may participate** as appropriate. The following members, **or their qualified designees**, are responsible for DLRT recommendations: investigators, Amgen medical monitor, and global safety officer**.**

All available study data, including data collected after the initial DLT window, and including demographics, IP 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), as well as **the** Amgen representatives **responsible for DLRT recommendations** listed above. **Investigators that are not able to participate in the meeting (eg, due to time difference) may also provide their vote in writing (eg, by email to Sponsor) after review of the data discussed at the meeting.** 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 infusions 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/D5/D12/D19 dosing scheme within the pre-specified window of +/- 1 day

· extension of the treatment-free interval between treatment cycles

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 the first 5 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment / study, whichever occurs earlier. Ad hoc meetings may be convened any time in case of important safety event

7.2 Primary Analysis

The primary analysis will occur when target enrollment is complete, and each subject had the opportunity to receive up to 2 cycles of treatment or terminated the study early

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.

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 a base.

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 A.
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.

The following imputation of missing values will be done:

- Incomplete adverse event and concomitant medication dates will be imputed as per Appendix A. If imputed dates are used, then they will be identified as such in the final study report.
- 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.
- Biomarker data that are below the quantification limits will be considered equal to half of the lower limit of quantification for all analyses unless specified 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.

A two-parameter Bayesian Logistic Regression Model (BLRM) is used to guide dose exploration. The maximum tolerated dose (MTD) target Toxicity Probability Interval (TPI) for dose-limiting toxicity (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 over-dose 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:

$$log\ [pi\ /\ (1\text{-}pi)] = logit(pi) = log[a] + exp(\ log[b])\ log\ (di\ /\ dref)$$

where a and b are random variables and dref 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 the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. **The prior distribution of BLRM for step dosing may be adjusted based on the accumulative data. For example, the starting dose and the reference dose of BLRM prior to estimate MTD2 may be based on MTD1 and the expected MTD for MTD2.** The operating characteristics of the 2-parameter BLRM design were evaluated via simulation for **schedule A and B separately.**

[redacted]

9.2 Subject Accountability

The number and percent of subjects who were screened, enrolled, received at least one dose of AMG 673, 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. A list of subjects screened but not enrolled (screen failures) 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.

9.4 Demographic and Baseline Characteristics

Demographic (ie, 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

Not Applicable

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Not Applicable

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Listings will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts indicating the time to progression, time to response, and duration of response Event free Survival . The proportion of subjects with a CR/CRh*/CRi/morphologic leukemia-free state with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD/**RP2D**. Kaplan Meier curve may be presented for time to progression with estimates for rates and 80% CI at selected weeks. Statistical analyses of efficacy endpoints will be considered exploratory.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Not Applicable

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

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 673.

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

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 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 criteria.

The severity of each CRS event will be graded according to the guidelines provided in Table 5 [based on the adopted grading system referenced in Lee et al (Blood 2014)] in the protocol.

Treatment-emergent adverse events are events with an onset after the administration of the first dose of investigational product.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.
Tables of disease-related events, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

Subject incidence of all disease-related events, fatal disease-related events, serious disease-related events, disease-related events leading to withdrawal from investigational product or other protocol-required therapies, and significant disease related events will also be provided. Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term. Subject incidence of first dose effects will be used to fit the BLRM model to estimate the probability of having an adverse event related to first dose effects across dose levels.

9.6.3 Laboratory Test Results

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

Additionally, the number and percentage of subjects experiencing **0,**1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

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

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

A summary of the change from baseline to the post dose maximum, time to post-dose maximum, change from baseline to the post dose minimum, and the time to the post dose minimum may also be provided for selected parameters of interest.

Below is list of all lab tests performed:

Local Laboratory					
Chemistry	Hematology	Urinalysis	Coagulation	Other Labs	Central Laboratory
Sodium	Erythrocytes	Specific	PT	Pregnancy	[redacted]
Potassium	Hemoglobin	gravity	PTT	test[a]	
Bicarbonate	Hematocrit	pH	INR	Serology	Pharmacokinetics
Or	MCV	Blood	Fibrinogen	(HepB,	Cytokines
Total CO_2	Platelets	Protein	AT III	HepC)	Blood
Chloride	WBC Differential	Glucose		Bone marrow	[redacted]
Total protein	Total Neutrophils	Bilirubin		cytology and	
Albumin	Seg. Neutrophils	Ketones		cytochemistry	
Calcium	Lymphocytes	Microscopic		Standard	
Magnesium	Atypical	exam		bone marrow	
Phosphorus	Lymphocytes	(performed		[redacted]	
Glucose	Monocytes	at the			
BUN	Bands/Stabs	discretion of			
Urea	Eosinophils	the			
Creatinine	Basophils	investigator)			
Total bilirubin	Blasts				
ALP	Myeloblasts				
AST	Monoblasts				
ALT	Megakaryoblasts				
Amylase	Promyelocytes				
Lipase	Myelocytes				
CRP	Metamyelocytes				
LDH	Nucleated RBC				
Uric Acid	Immature				
Ferritin	Granulocytes				

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBc = Hepatitis B core antibody; AST = aspartate aminotransferase; AT III = Antithrombin III; CRP = C-reactive protein; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; INR = international normalize ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; MRD = Minimal Residual Disease; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell

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

9.6.4 Vital Signs

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

9.6.5 Physical Measurements

The change in weight from baseline to each scheduled assessment time point will be summarized.

9.6.6 Electrocardiogram

All on-study electrocardiogram (ECG) data will be listed and select parameters of interest may be plotted.

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

The analysis of Fridericia's (QTcF) QT correction will use the results recorded on the CRF. Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change.

- <=30 msec
- >30 – 60 msec
- >60 msec

The number and percentage of subjects in each group will be summarized.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- <=450 msec
- >450 – 480 msec
- >480 – 500 msec
- >500 msec

The number of subjects in each group will be summarized for each dosing group.

[redacted]

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule. The number of cycles, Total Number of Non-Zero Doses, number of doses of investigational product and the total dose in µg will be summarized.

9.6.9 Exposure to Non-investigational Product

Not Applicable

9.6.10 Exposure to Other Protocol-required Therapy

Not Applicable

9.6.11 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. A subject listing of all prior and concomitant medications will be presented.

9.7 Other Analyses

All exploratory endpoints will be described in Supplemental Statistical analysis plan (SSAP) as applicable.

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Serum concentrations of AMG 673 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}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) and clearance. 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 673 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 673 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

9.7.2 Analyses of Clinical Outcome Assessments

Not Applicable

9.7.3 Analyses of Health Economic Endpoints

Not Applicable

9.7.4 Analyses of Biomarker Endpoints

Not Applicable

10. Changes From Protocol-specified Analyses

Time to Progression endpoint in protocol refers to Event Free Survival, to address the Relapse/refractory AML subjects who are already in progressive state and never respond.

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

12. Prioritization of Analyses

Not Applicable

13. Data Not Covered by This Plan

Not Applicable

14. Appendices

Appendix A. 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 death date is in error, do not impute and censor the subject survival time.]

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.

Appendix C. Summary of Changes

Section: Study Design

Replace:

This is a first-in-human, open-label, phase 1, sequential dose escalation study. AMG 673 will be evaluated as a short term intravenous (IV) infusion in adult subjects with relapsed/refractory AML. The study will be conducted at approximately 7 sites in Australia, Germany and the United States. Additional sites may be added later.

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 673. Planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 0.05 µg, 0.15 µg, 0.45 µg, 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the first cohort will be 0.05 µg administered as short term IV infusions on D1 and D5. The doses administered for the cohorts following cohort 1 will be recommended by the Dose Level Review Team (DLRT). The DLRT may recommend on the administration of up to 2 additional infusions on D12 and D19 of a cycle for a future cohort. All subjects will be pre treated with an 8-mg dose of IV dexamethasone 1 hour prior to day 1 and day 5 AMG 673 doses and prior to each step-up dose of AMG 673. Each cycle will last for 14 days in the cohorts receiving only 2 doses (Day 1, 5) and 28 days in the cohorts receiving 4 doses (Day 1, 5, 12, 19). This cycle will be followed by a treatment-free interval for 2 weeks, which may be extended for up to 5 weeks or longer for the cohorts at higher doses, based on a DLRM recommendation. The D5 infusion, and the D12/D19 infusions (if applicable) may be at the same dose as the preceding infusion 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 3 in Section 3.1. There is a ± 1 day window for dosing visits which may be implemented after consultation with the sponsor.

With:

This is a first-in-human, open-label, phase 1, sequential dose escalation study. AMG 673 will be evaluated as a short term intravenous (IV) infusion in adult subjects with relapsed/refractory AML. The study will be conducted at approximately **10** sites in Australia, Germany and the United States. Additional sites may be added later.

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and pharmacodynamics (PD) **using 2 schedules** of AMG 673 **administration: Schedule A (D1/D5 dosing) and Schedule B (QD dosing for cycle 1 followed by twice weekly dosing in following cycles).**

For Schedule A, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 0.05 µg, 0.15 µg, 0.45 µg, 1.5 µg, 4.5 µg, 9 µg, 18 µg, 36 µg, 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the first cohort will be 0.05 µg administered as short term IV infusions on D1 and D5. The doses administered for the cohorts following cohort 1 will be recommended by the Dose Level Review Team (DLRT). The DLRT may recommend on the administration of up to 2 additional infusions on D12 and D19 of a cycle for a future cohort. All subjects will be pre treated with an 8-mg dose of IV dexamethasone 1 hour prior to day 1 and day 5 AMG 673 doses and prior to each step-up dose of AMG 673. Each cycle will last for 14 days in the cohorts receiving only 2 doses (Day 1, 5) and 28 days in the cohorts receiving 4 doses (Day 1, 5, 12, 19). **Each** cycle will be followed by a treatment-free interval for **0 to 14 days depending on treatment response and recovery of blood counts, but may be extended as described in Section 6.2.1.1.1 after consultation with Sponsor**. The D5 infusion, and the D12/D19 infusions (if applicable) may be at the same dose as the preceding infusion 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**. There is a ± 1 day window for dosing visits which may be implemented after consultation with **S**ponsor.

For Schedule B, planned dose levels (dose per infusion) for the dose escalation cohorts are as follows: 72 µg, 110 µg, 160 µg, 240 µg, 360 µg and higher if MTD is not reached. The starting dose for the cohort 1 on Schedule B will be 72 µg administered as short-term IV infusions daily (QD) during the 14-day cycle 1 after the 72 µg target dose is found to be relatively safe and tolerable by the DLRT for Schedule A. Cohort 2 and higher will include step-up doses added in each cohort administered in two day increments after the previous step dose up to the target dose in cycle 1 (eg, cohort 2 will start with 72 µg for 2 days followed by 110 µg administered on D3 to D14; cohort 3 will start with 72 µg for 2 days followed by 110 µg on D3 for 2 days followed by 150 µg on D5 to D14, etc). Cycle 2+ doses will be given on days 1, 4, 8 and 11 at the target dose. See Table 3 and Section

6.2.1.1.2 for Schedule B dosing schema by cohort. All subjects will be pre treated with an 8-mg dose of IV dexamethasone 1 hour prior to the first dose on day 1 and prior to each step-up dose in cycle 1 and prior to all doses in cycle 2 and beyond. There is no treatment free interval between cycle 1 and cycle 2. Beyond cycle 2, a treatment-free interval is allowed for 0 to 14 days depending on treatment response and recovery of blood counts, and may be extended as described in Section 6.2.1.1.1 after consultation with the sponsor. Adjustments to dose level, dose frequency and a duration of step dosing may be considered after recommendation of DLRT based on review of available safety, PK, and PD data.

Section: Study Design, Dose Escalation Cohorts

Replace:

Dose Escalation will be conducted in 2 stages: a single subject stage and a multiple subjects stage. In the single subject cohorts, cohorts 1 and 2, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events related to AMG 673 will be observed. Multiple subject cohorts, starting with cohort 3, will enroll and the cohort size will be extended to 3-4 subjects per cohort. The Bayesian logistic regression model (BLRM) design will be used to guide dose escalation. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the dose level review team (DLRT) after considering all information. Subjects will be assessed for dose limiting toxicities (DLTs) for the duration of their treatment cycle ie, 2 weeks from D1 for subjects who receive 2 doses and 4 weeks for subjects who receive 4 doses. 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 and no ≥ grade 3 adverse event(s), deemed treatment related by the investigator, are reported for that subject.

With:

Dose Escalation will be conducted in 2 stages: a single subject stage **(Schedule A only)** and a multiple subjects stage. In the single subject cohorts, cohorts 1 and 2, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events related to AMG 673 will be observed. Multiple subject cohorts, starting with cohort 3, will enroll and the cohort size will be extended to 3-4 subjects per cohort. The Bayesian logistic regression model (BLRM) design will be used to guide dose

escalation. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the dose level review team (DLRT) after considering all information. Subjects will be assessed for dose limiting toxicities (DLTs) for the duration of their **first** treatment cycle **(**ie, 2 weeks from D1 for subjects who receive 2 doses and 4 weeks for subjects who receive 4 **doses in Schedule A and 4 weeks from D1 for subjects in Schedule B).** Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle **after** the next dose **level** has been deemed safe by the **DLRT, after consultation with Sponsor, if no DLT was reported for that subject** and no ≥ grade 3 adverse event(s), deemed treatment related by the investigator, are reported for that subject.

Section: Study Design, Estimation of initial and target MTDs

Replace:

It is anticipated that 2 MTDs may be estimated, one for the initial dosing and one for the subsequent dosing. Should the initial dose be limited by adverse events related to first dose effects, the second MTD for the target dose will be estimated after giving the initial dose at MTD (dose step). 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.

With:

For Schedule A, it is anticipated that **at least** 2 MTDs may be estimated, one for the initial dosing and one for the subsequent **step** dosing. Should the initial dose be limited by adverse events related to first dose effects, the second MTD for the target dose will be estimated after giving the initial dose at MTD (step dose). 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.

Schedule B will be initiated after preliminary safety data of AMG 673 in Schedule A (eg, MTD1 is estimated to be ≥72 µg) become available and may be conducted in

parallel with Schedule A per Sponsor's decision. The MTD for Schedule B will be estimated following the dose escalation described in Section 6.2.1.1.2 and guided by BLRM described above.

Section: Study Design, Expansion Cohort

Replace:

At completion of the dose escalation cohorts, additional subjects (up to 10) will be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. Additional expansion cohorts may be covered by a protocol amendment to test alternative dose levels or biologic subsets.

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.

With:

For each Schedule, upon completion of the dose escalation cohorts, additional subjects (up to 10) **may** be enrolled in a dose expansion cohort to gain further clinical experience, safety and efficacy data in subjects with AMG 673. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. Additional expansion cohorts may be covered by a protocol amendment to test alternative dose levels or biologic subsets.

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 **for each schedule**.

Section: Sample Size

Replace:

It is anticipated that approximately 50 subjects will be enrolled in this study. Approximately 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort. 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.

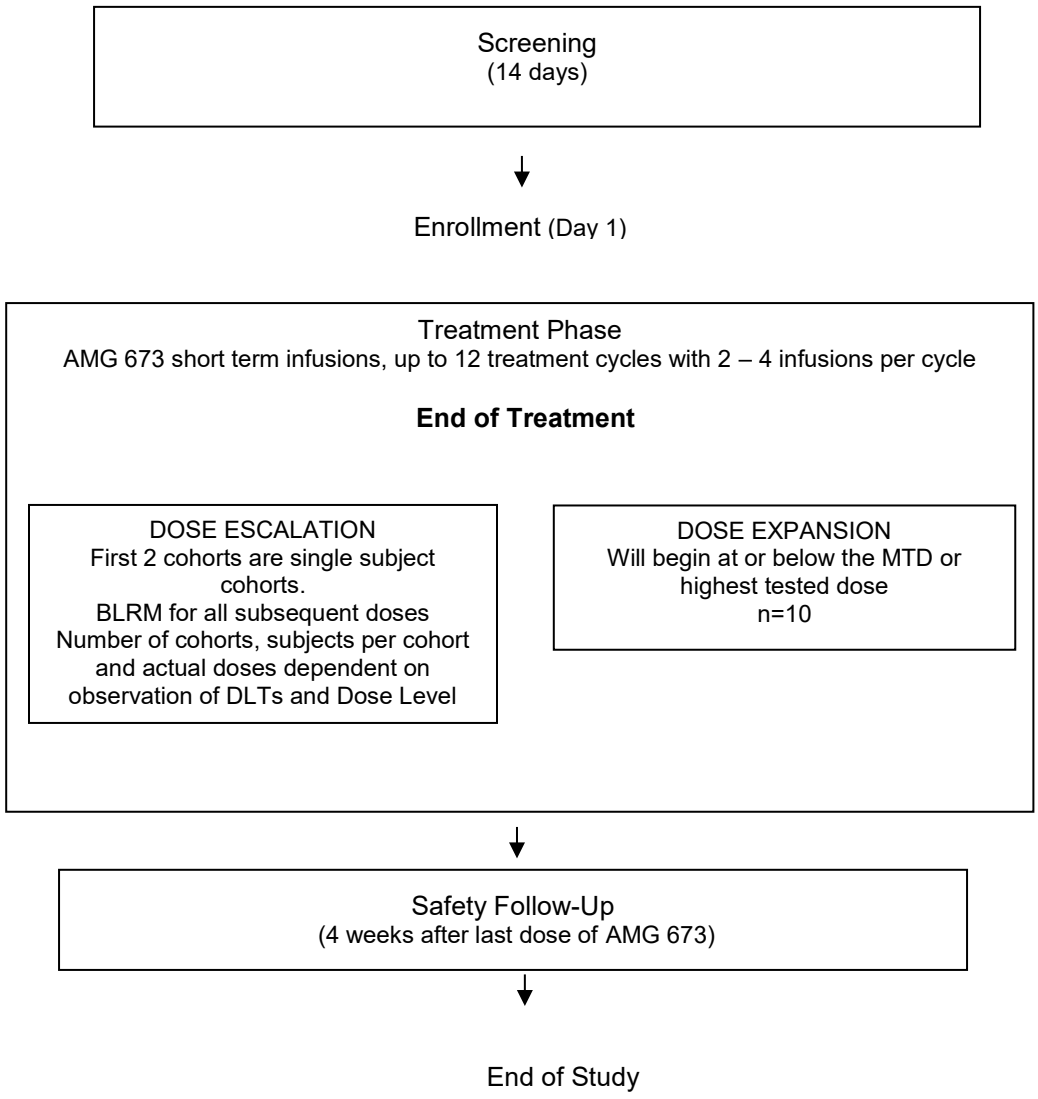
With:

It is anticipated that approximately **95** subjects will be enrolled in this study. **For Schedule A, a**pproximately 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort. **For Schedule B, up to 40 subjects will be enrolled in the dose escalation cohorts and up to 10 additional subjects will be enrolled in the dose expansion cohort.** For ethical and operational reasons subjects who already are in the screening phase at the time of enrollment stop (end of expansion phase) **may** still be allowed to be treated. Therefore, an over running of subject recruitment might be possible.

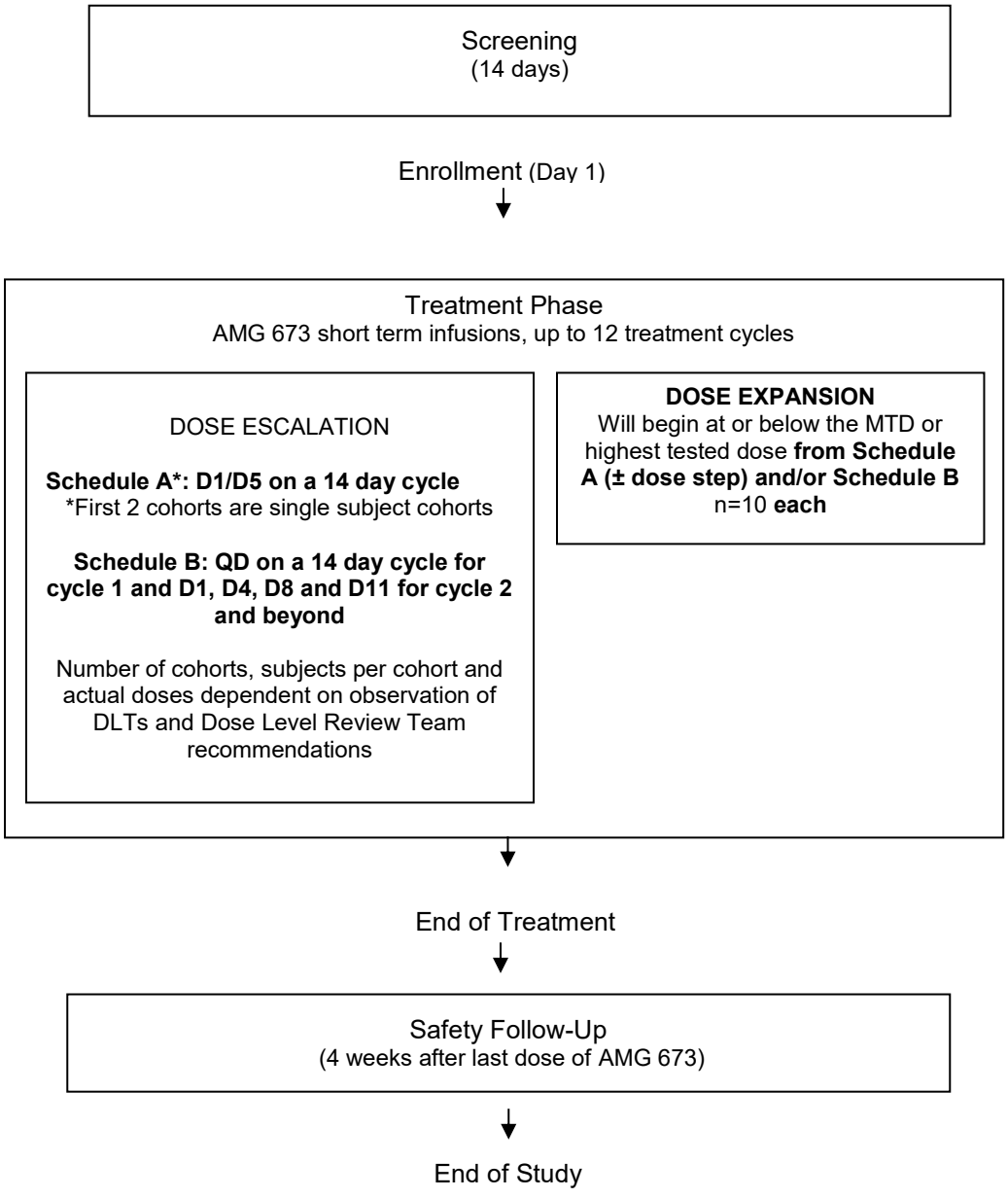
Based on emerging data, additional subjects may be enrolled **or a schedule may be discontinued**.

Section: **Study Design and Treatment Schema, Treatment Phase**

Replace:



With:


Screening
(14 days)
Enrollment (Day 1)
Treatment Phase
AMG 673 short term infusions, up to 12 treatment cycles
DOSE ESCALATION
Schedule A*: D1/D5 on a 14 day cycle
*First 2 cohorts are single subject cohorts
Schedule B: QD on a 14 day cycle for cycle 1 and D1, D4, D8 and D11 for cycle 2 and beyond
Number of cohorts, subjects per cohort and actual doses dependent on observation of DLTs and Dose Level Review Team recommendations
DOSE EXPANSION
Will begin at or below the MTD or highest tested dose from Schedule A (± dose step) and/or Schedule B
n=10 each
End of Treatment
Safety Follow-Up
(4 weeks after last dose of AMG 673)
End of Study

Section 5: Definitions

Replace:

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, as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to end of study (EOS).

Duration of Response (DOR)

Duration of response is defined as the number of days between the date of the first tumor assessment indicating an objective response through to the subsequent date of progression as defined by revised IWG response criteria (Appendix E in the protocol) or death due to any cause, or where applicable date of censoring [date of first progressive disease assessment or death or date of censoring – date of the first objective response result +1]. Subjects who respond and have not progressed while on study will be censored at the date of assessment of the last evaluable tumor assessment. Subjects who do not achieve an objective response will be excluded from the analysis of duration of response. Objective Response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi) or morphologic leukemia-free state (all according to Revised International Working Group [IWG] response criteria) or CR with partial hematologic recovery (CRh*).

Time to Response (TTR)

Time to response defined as the interval from the first administration of AMG 673 to the first documentation of confirmed response. Response is defined as any of the following: complete remission (CR), CR with incomplete recovery (CRi) or morphologic leukemia-free state (all according to Revised International Working Group [IWG] response criteria) or CR with partial hematologic recovery (CRh*). Time to response is calculated as the number of days: (date of first response – date of study day 1 +1).

With:

Treatment-Emergent Adverse Event (TEAE)

Treatment-emergent adverse events are events categorized as Adverse Events (AEs) **including disease related events** starting on or after the first dose of investigational

product, as determined by the flag indicating if the adverse event started prior to the first dose on the Events CRF and up to end of study (EOS).

Duration of Response (DOR)

Duration of response is defined as the interval from the date of the first disease assessment indicating an overall response to the first documented relapse or death due to any cause, whichever occurs first. Subjects without relapse or death until the analysis data cut-off date will be censored at the last adequate disease assessment date. Only subjects with a response will be evaluated for DOR.

DOR time in days = earlier of (date of first relapse or disease progression or death or date of censoring) – date of the first observation of overall response + 1.

Time to Response (TTR)

Time to response defined as the interval from the first administration of AMG 673 **to the first documentation of response. Time to response is evaluated only for subjects who achieved a response.**

Time to response is calculated as the number of days:
(**date of first response** – date of study day 1 + 1).

Added:

Dose Limiting Toxicities (DLT)

DLT will be determined by "Is this event a Dose Limiting Toxicity (DLT)?" equal to "Yes" on the Events eCRF. Investigators will determine whether an adverse event qualifies as a DLT per protocol Section 6.2.1.3

Overall Response

Overall response is defined as achieving any of the following response: CR, CRh*, CRi or MLFS.

Time to Progression (Event-free Survival):

Event-free survival (EFS) is defined as the interval from first administration of AMG 673 to the earliest of date of treatment failure, relapse for responders, or death due to any cause. Censoring is at the last evaluable post-baseline response assessment; otherwise, at first administration of AMG673. For non-responders, the event date for treatment failure is assigned as the date of first administration of AMG 673.

Event-free Survival in days = earlier of (date of treatment failure or relapse or death or date of censoring) – date of the first administration of AMG 673 + 1.

Removed:

Dose Limiting Toxicities (DLT)

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 infusion) and last for 14 days for cohorts receiving 2 doses (i.e. Day 1 and Day 5 dose) and for 28 days for subjects receiving 4 doses (i.e. Days 1,5,12,19). The CTCAE will be used to assess toxicities/adverse events with the exception of CRS (see Table 5 in protocol for grading of CRS).

Section: 7.1 Dose Level Review Team (DLRT)

Replace:

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.

With:

The DLRT will be composed of the investigators or designees, and the following Amgen representatives: early development leader**/Medical Monitor and** global safety officer, or **their approved** designee**s**, clinical study manager, **and** biostatistician **and** PK scientist (optional). **O**ther functional area representatives **may participate** as appropriate. The following members, **or their qualified designees**, are responsible for DLRT recommendations: investigators, Amgen medical monitor, and global safety officer**.**

Section7.1 Dose Level Review Team (DLRT)

Replace:

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.

With:

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), as well as **the** Amgen representatives **responsible for DLRT recommendations** listed above. **Investigators that are not able to participate in the meeting (eg, due to time difference) may also provide their vote in writing (eg, by email to Sponsor) after review of the data discussed at the meeting.** 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.

Section 9: General consideration:

Replace:

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 the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. These values were selected such that $p_i = 0.02$ for the starting dose, and $p_i = 0.3$ for d_{ref}, where 0.3 is approximately the middle of the target TPI and d_{ref} is the dose that is expected to be the MTD.

With:

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 the lowest planned dose is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose is 0.05. **The prior distribution of BLRM for step dosing may be adjusted based on the accumulative data. For example, the starting dose and the reference dose of BLRM prior to estimate MTD2 may be based on MTD1 and the expected MTD for MTD2.** The operating characteristics of the 2-parameter BLRM design were evaluated via simulation **for schedule A and B separately**.

For schedule A, we evaluated the operation characteristics of the two-parameter BLRM design for no dose step schedule. Since it is unlikely to observe toxicity at the lowest dose levels, simulations use 0.45 µg as the initial dose level. The 0.45 µg dose

level is anticipated to be the starting level for the multiple subject cohorts**. In addition, we assume that p_i = 0.02 for the starting dose, and p_i = 0.3 for d_{ref}, where 0.3 is approximately the middle of the target TPI and d_{ref} is the dose that is expected to be the MTD.**

- **For schedule B, simulations use 72 µg as the initial dose level and we assume that p_i = 0.05 for the starting dose, and p_i = 0.3 for d_{ref}, where 0.3 is approximately the middle of the target TPI and d_{ref} is the dose that is expected to be the MTD.**

Section:9.6.3 Laboratroty Test Results
Replace:

Additionally, the number and percentage of subjects experiencing 1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

With:

Additionally, the number and percentage of subjects experiencing **0,**1, 2, 3 and 4 worsening CTCAE grade shifts from baseline will be presented. The direction of the laboratory worsening will again be denoted.

Removed:

The number and percentage of subjects experiencing treatment emergent laboratory toxicities with worst post dose CTCAE grades of ≥1, ≥2, ≥3 and 4 will be presented. The direction of the laboratory worsening will be denoted. The summary will be presented for all laboratory parameters for which at least one subject experienced a treatment emergent toxicity with a worst grade ≥ 3.

A listing of CTCAE grade 3 or higher laboratory toxicities will be provided. This listing will include all laboratory data for the subject and laboratory parameter of interest in order to provide proper context. A flag will indicate the grade 3 or higher toxicity.

Section:9.6.8 Exposure to investigational product

Replace:

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule. The number of cycles, number of doses of investigational product and the total dose in µg will be summarized

With:

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule. The number of cycles, Total Number of Non-Zero Doses, number of doses of investigational product and the total dose in µg will be summarized.

Section: Other Protocol Required Therapies

Add:

Time to Progression endpoint in protocol refers to Event Free Survival, to address the Relapse/refractory AML subjects who are already in progressive state and never respond.

Appendix A.

Replace:

Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the 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 a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

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.

Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

With:

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 death date is in error, do not impute and censor the subject survival time.]

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.