Statistical Analysis Plan

Protocol Title:	A Phase 1 First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 330 Administered as Continuous Intravenous Infusion in Subjects with Myeloid Malignancies
Short Protocol Title:	A Phase 1 First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 330 Administered as Continuous Intravenous Infusion in Subjects with Myeloid Malignancies
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	22Jul2015	NA
Amendment 1 (v2.0)	29 October 2021	• Inclusion of design and analysis for new Groups to be consistent with protocol: MRD+AML (Group 2), MDS (Group 3), alternative CRS prophylaxis for R/R AML (Group 4 and Group 5) • Clarification of some definitions, such as treatment-emergent adverse event (TEAE), duration of response (DOR), time to response (TTR), event-free survival (EFS). Addition of overall survival endpoint. • Clarification of analysis sets, such as Dose Limiting Toxicity Evaluable (DLT-Evaluable) Analysis Set • Other administrative changes • Detailed Summary of changes provided in the Appendix C.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
CTCAE	Common Terminology Criteria for Adverse Events
DLRM	Dose-Level Review Meeting
ECG	Electrocardiogram
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MTD	Maximum tolerated dose
QTcB	Bazett-corrected QT Interval (QTcB)
QTcF	Fridericia-corrected QT Interval (QTcF)
RP2D	Recommended phase 2 dose
R/R AML	Relapsed or refractory AML
Study Day 1	Defined as the first day that investigational product(s) is administered to the subject
µg	Microgram

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within Protocol Amendment 9 (for study 20120252, AMG 330 dated 15 February 2021). The scope of this plan includes the interim analysis, primary analysis, and final analysis that will be executed by the Amgen Global Biostatistical Science department unless otherwise specified. PK/PD and biomarker analyses will be provided by Clinical Pharmacology, Modeling and Simulation (CPMS) group and clinical biomarker group in Department of Translational Medicine.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Primary Objectives:

- Evaluate the safety and tolerability of AMG 330 in adult subjects with relapsed/refractory AML, MRD+ AML and MDS
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)] of AMG 330 in adult with relapsed/refractory AML, MRD+AML and MDS

Secondary Objectives:

- Evaluate the pharmacokinetics (PK) of AMG 330
- Determine the formation of anti-AMG 330 antibodies
- Evaluate the anti-leukemia activity of AMG 330 by evaluating
  - the number and proportion of subjects who respond to treatment with AMG 330. 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 number and proportion of subjects with MDS who respond to treatment with AMG 330. Response is defined as any of the following: CR or marrow CR (all according to Revised IWG response criteria).
  - the number and proportion of subjects with MRD-positive AML (Group 2) who respond to treatment with AMG 330. Response is defined as conversion from MRD+ status with 0.1% threshold to MRD- status

- the duration of response, event-free survival, time to response, and overall survival

Exploratory Objectives:

- Evaluate the protein, nucleic acid, and cellular biomarkers in blood and / or bone marrow, as applicable [eg, cytokines, lymphocyte subsets, minimal residual disease (MRD – Group 1 only), leukemic stem cells (LSCs)]
- Evaluate effects of genetic variations in and phenotype of cancer genes, including apoptotic markers, on adverse event profile and treatment response
- Evaluate mechanisms of resistance
- Evaluate potential measures of clinical benefit including number of blood products transfused and days of antibiotic treatment of infection
- Evaluate the relationship between AMG 330 exposure and response to treatment
- [redacted]
- Explore the additional thresholds of conversions to MRD- status in MRD+ AML subjects as an efficacy measure for AMG 330 treatment

Primary Endpoint:

- Safety: subject incidence and grade of adverse events (AEs) and dose limiting toxicities (DLTs)

Secondary Endpoints:

- Pharmacokinetic parameters: half-life, steady state concentration, volume of distribution and clearance of AMG 330
- Incidence of anti-AMG 330 antibody formation
- Efficacy parameters for R/R AML: response rate (response defined as CR/CRi/morphologic leukemia-free state [per modified IWG criteria] or CRh), duration of response, time to response, event-free survival and overall survival (duration of response, event-free survival, and overall survival will only be measured in the expansion cohort)
- Efficacy parameters for MRD-positive AML: response rate (response defined as conversion from MRD+ status with 0.1% threshold to MRD-), time to response,

relapse-free survival, and overall survival (relapse-free survival and overall survival will only be measured in the expansion cohort)

- Efficacy parameters for MDS: response rate (response defined as CR or marrow complete remission [per International Working Group (IWG) standardized response criteria]), duration of response, time to response, event-free survival and overall survival (duration of response, event-free survival, and overall survival will only be measured in the expansion cohort)

Exploratory Endpoints:

- Depletion of LSCs
- MRD response
- Lymphocyte counts, cluster of differentiation (CD) 33+ monocytes and T cells, as well as T cell activation (including T cell subsets). Other immune subsets may also be examined
- [redacted]
- [redacted]
- Changes in serum cytokine levels
- Frequency and severity of cytokine release syndrome (CRS) and other AEs following [redacted] premedication, and alternative dose step schedules of AMG330
- [redacted]

2.2 Hypotheses and/or Estimations

AMG 330 will demonstrate evidence of anti-leukemic activity at a well-tolerated dose in subjects with AML and MDS.

3. Study Overview

3.1 Study Design

This is a first-in-human, open-label, phase 1 sequential dose escalation study. AMG 330 will be evaluated as a continuous intravenous (cIV) infusion in adult subjects with relapsed/refractory (R/R) AML (Group 1), MRD+ AML (Group 2) and MDS (Group 3). The study will be conducted at approximately 17 sites in Germany, the Netherlands, Japan, Canada and the United States.

The dose-escalation cohorts will estimate the MTD/biologically active dose, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 330.

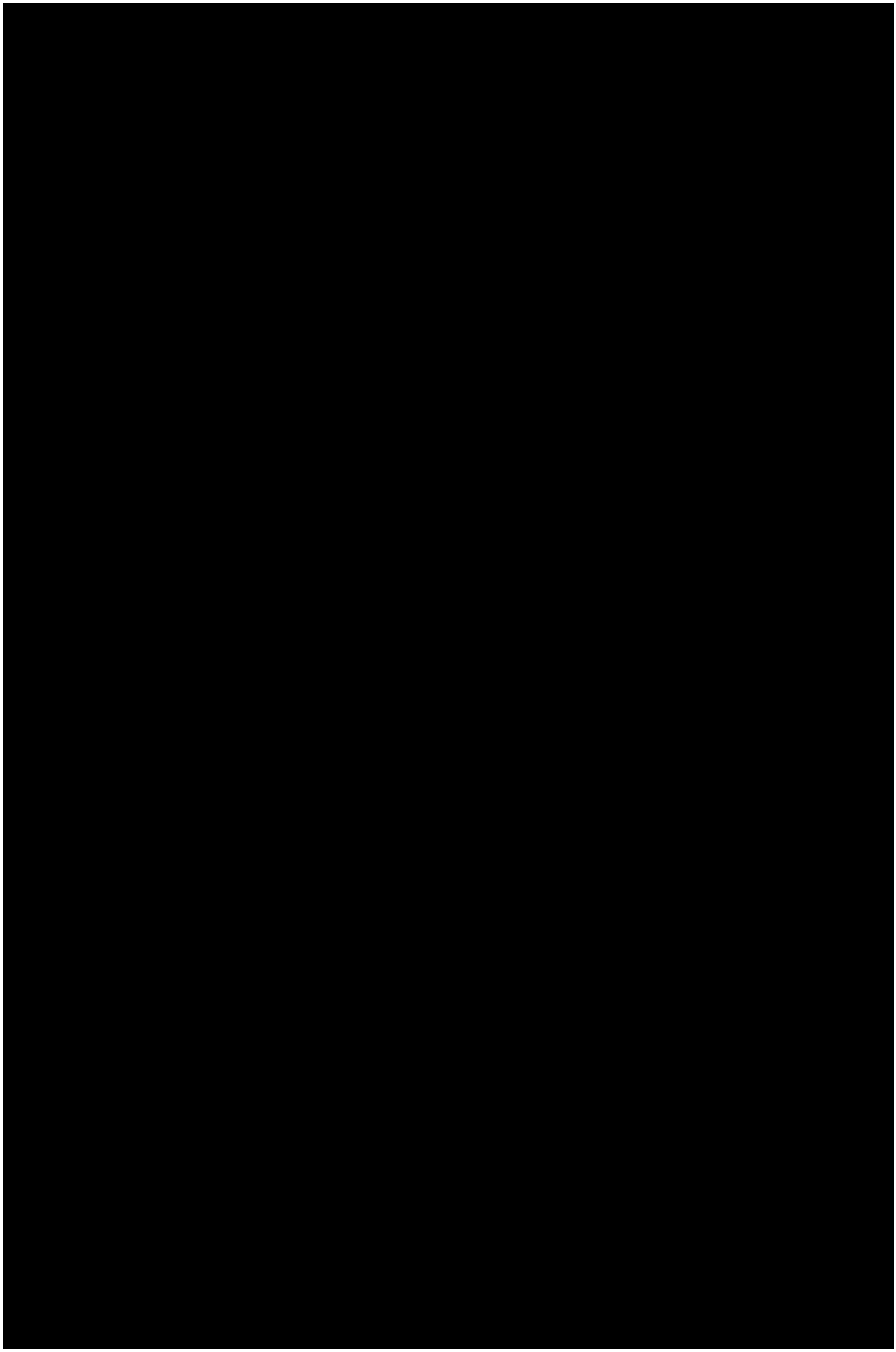
For R/R AML (Group 1), planned dose levels for the dose-escalation cohorts are as follows: 0.5, [redacted] and 960 µg/day. Intermediate and/or higher dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary to reach MTD. The same dose level may be tested in multiple cohorts, but with different dose steps and/or different cycle lengths.

For MRD+ AML (Group 2), planned target dose levels for the dose-escalation cohorts are as follows: [redacted] and 960 µg/day. Each target dose level will be preceded by dose steps. Intermediate dose steps and additional target dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary. Escalation can continue until the biologically active dose for MRD+ AML is established. Selected target dose levels, with the exception of the maximal tested dose, that have been deemed safe in subjects with R/R AML (Group 1) could be skipped in Group 2 phase 1a dose escalation cohorts based on available safety, PK, and PD data if recommended by the Dose Level Review Team (DLRT).

For MDS (Group 3), planned target dose levels for dose-escalation cohorts are as follows: [redacted] and 960 µg/day. Each target dose will be preceded by dose steps. Intermediate dose steps and additional dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary. Escalation can continue until MTD for MDS is established. Selected target dose levels, with the exception of the maximal tested dose, that have been deemed safe in subjects with R/R AML (Group 1) could be skipped in Group 3 phase 1a dose escalation cohorts based on available safety, PK, and PD data if recommended by the DLRT.

It is anticipated that more than one MTD may be estimated, one for each dose step and one for the target dose. Should the initial dose be limited by adverse events related to first dose effects (eg, cytokine release syndrome [CRS]), the second MTD for the target dose will be estimated after giving the initial dose at MTD (dose step). Starting with cohort 6 (R/R AML, Group 1), a dose step in each cycle is mandatory for all newly enrolled subjects. Administration of a prophylactic steroid dose (8 mg IV dexamethasone) within 1 hour prior to the dose step for prevention of cytokine release is mandatory. The additional assessments described in the schedule of assessments for dose steps (in Protocol Table 14) apply.

[redacted]



[redacted]

Dose Escalation:

For Group 1 (R/R AML), dose escalation will be conducted in two stages. In the single subject cohorts, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events related to AMG 330 will be observed. Once higher dose levels are open for enrollment or drug related safety or efficacy signals are observed, multiple subject cohorts of up to 6 subjects per dose level will open for enrollment (3+3 design). Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle if no DLT has been reported for either this subject or any other subject in this dose cohort after completion of the DLT period, and once the next dose cohort is open for enrollment. (see Section 7.2.2 in protocol for details on assessments applicable in case of intra-subject dose escalation).

In Group 1 (R/R AML), should the initial dose be limited by adverse events related to first dose effects (eg, CRS), dose steps will be implemented. An optimal dose step schedule and MTD for the target dose will be estimated following decision rules.

For Groups 2 and 3 (MRD+ AML and MDS), each dose escalation cohort will enroll a minimum of 3 to a maximum of 9 evaluable subjects. Dose escalation will be guided by a modified toxicity probability interval approach (mTPI-2; Guo et al, 2017). The DLRT will review all available safety, laboratory, PK and PD data and provide dose-finding recommendations.

For Groups 1, 2 and 3, enrollment will occur simultaneously, and each Group will progress from the dose escalation to the dose expansion independently. The total number of subjects to be enrolled for the dose escalation will depend on the toxicities observed as the study progresses. Additional subjects may be required if other dose levels or alternate treatment schedules are explored.

Enrollment in Group 4 is independent from enrollment in Groups 1, 2 and 3. For Group 4, enrollment in Arm 1 will occur first. Once all subjects in Arm 1 have initiated treatment, enrollment into Arm 2 will begin. Once all Group 4 subjects have completed the DLT period, enrollment into Group 5 can commence. If there are 2 arms in Group 5, all subjects in Arm 1 must have initiated treatment before enrollment into Arm 2 can begin.

Expansion Cohorts:

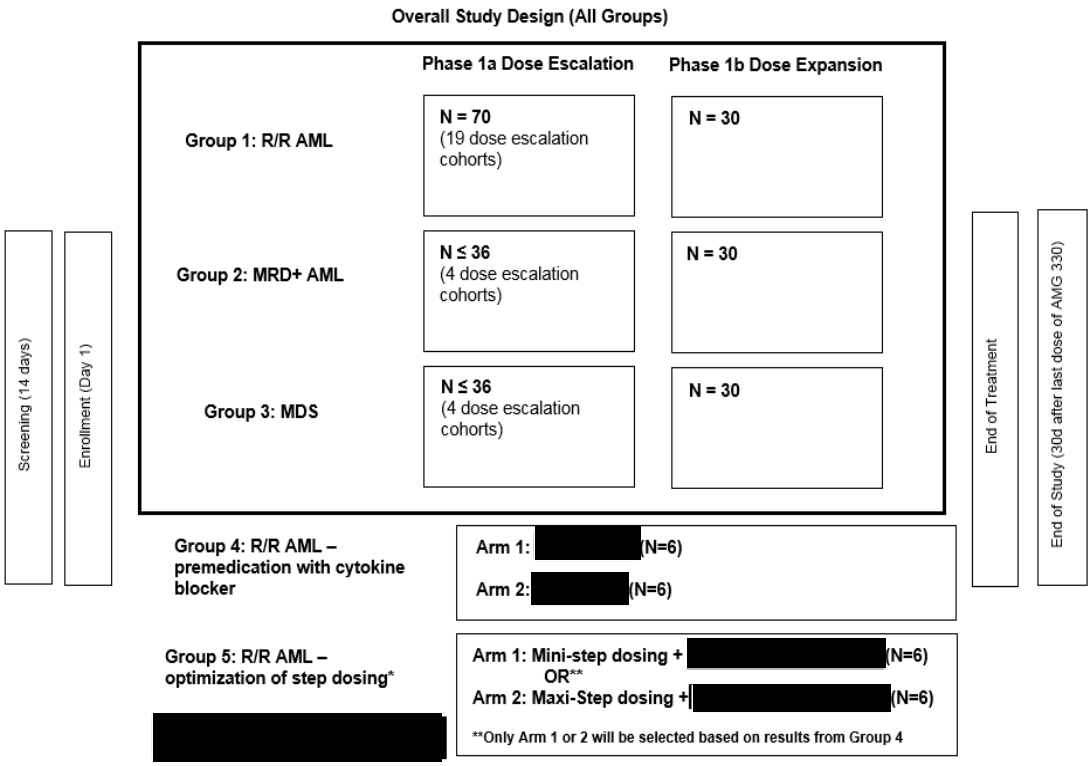
At completion of the dose escalation cohorts, additional subjects will be enrolled in dose expansion cohorts to gain further clinical experience, safety and efficacy data in subjects with AMG 330. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. If there is at least 1 responding subject in the first 10 subjects enrolled in the expansion cohort, additional (up to 20) subjects will be enrolled after evaluating safety, tolerability and anti-leukemia activity of AMG 330 using all available cumulative data. Additional expansion cohorts testing alternative dose levels or biologic subsets may be considered by amendment.

For each Group, a final estimate of the MTD and/or RP2D will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose escalation and the dose expansion cohorts.

Study Schema:

The overall study design is described by a study schema at the end of the protocol synopsis and below (Figure 1).

Figure 1. Study Design and Treatment Scheme



3.2 Sample Size

It is anticipated that approximately 256 subjects will be enrolled in this study. For the dose escalation cohorts, approximately 70 subjects will be enrolled in Group 1 (R/R AML), up to 36 subjects will be enrolled in Group 2 (MRD+) and up to 36 subjects will be enrolled in Group 3 (MDS). Up to 30 additional subjects will be enrolled in a dose expansion cohort for each group (up to 90 additional subjects total). Approximately 24 subjects will be enrolled in the Groups 4 and 5, 6 subjects for each arm in Group 4 and 6-12 subjects in Group 5.

The sample size in the dose escalation is based on practical considerations and it is consistent with conventional oncology studies with the objective to estimate the MTD. With 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 6 subjects per cohort, there is a 47-91% probability.

In the dose expansion cohorts, a subject number of 10 will provide a 65% probability of observing at least one adverse event with10% incidence rate and 89% probability of observing at least one adverse event with 20% incidence rate.

Assuming a response rate of less than 5% and at least one subject having a response in the first 10 subjects for the enrollment to continue in the expansion cohort, there is greater than 59% chance of stopping the expansion cohort.

Assuming a response rate of greater than 20% and at least one subject having a response in the first 10 subjects for the enrollment to continue in the expansion cohort, there is less than 11% chance of stopping the expansion cohort. A sample of 30 subjects would provide a 96% probability of observing at least one adverse event, when the incidence of the adverse event is 10%. A sample of 30 subjects would provide a 100% probability of observing at least one adverse event, when the incidence of the adverse event is 20%. 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%.

Assuming a sample of 30 subjects and 20% overall response rate, the expected 80% CI would be 10.9% to 32.5% with the half-width 10.8%.

3.3 Adaptive Design

For MRD+ AML (Group 2) and MDS (Group 3), dose exploration will be guided by pre-specified monitoring rules, which is based on a modified toxicity probability interval algorithm (mTPI-2; Guo et al, 2017) with a target DLT rate of 25% and an acceptable

toxicity probability interval of 20%-30%. Consistent with conventional oncology phase 1 study designs (eg, 3 + 3 design) and given the imprecision with making decisions using as few as 3 subjects, in the instance of 1 DLT in the initial 3 subjects at a dose level then, as appropriate, the design allows expansion at the dose level beyond 3 subjects.

The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. Let p_T be the target toxicity level and ($p_T - \epsilon_1$, $p_T + \epsilon_2$) be the equivalence toxicity interval denoted as EI. The unit toxicity interval (0, 1) is divided into subintervals with equal length given by ($\epsilon_1 + \epsilon_2$). Let the under-dosing intervals (LI) denote for a set of intervals below EI, and the overdosing intervals (HI) for a set of intervals above EI. The 3 types of dosing intervals (EI, LI, HI) are associated with 3 different dose escalation decisions. The LI correspond to a dose escalation (E), the HI correspond to a dose de-escalation (D), and proper dosing intervals (EI) correspond to staying at the current dose (S). This study design uses a target toxicity level, p_T of 25%, and EI of (20%, 30%).

Decision rules are based on the unit probability mass (UPM) calculated on these equal-length intervals. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI-2 design calculates the UPMs for the each of equal-length dosing intervals. If the interval with the largest UPM is from LI, EI or HI, then the corresponding dose decision would be E, S, or D, respectively.

A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate p_T (ie, P [DLT > p_T | data] > 95%) with at least 3 evaluable subjects treated and evaluated at that dose level.

After the escalation phase is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010). The MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 25%. In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 25%, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity ≤ 25% will be selected, unless all tied

dose levels have estimated toxicity >25%, in which case the lowest dose level will be selected.

mTPI-2 Trial Monitoring Table

Number of DLTs	n=3	n=4	n=5	n=6	n=7	n=8	n=9
0	E	E	E	E	E	E	E
1	S[a]	S	S	E	E	E	E
2	D	D	D	D	S	S	E
3	DU	DU	DU	D	D	D	D
4	.	DU	DU	DU	DU	DU	D
5	.	.	DU	DU	DU	DU	DU
6	.	.	.	DU	DU	DU	DU
7	.	.	.	.	DU	DU	DU
8	.	.	.	.	.	DU	DU
9	.	.	.	.	.	.	DU

DLT = dose-limiting toxicity; E = escalate to the next higher dose level; S = stay at the current dose level; D = de-escalate to the next lower dose level; DU = current dose is unacceptably toxic; mTPI = modified toxicity probability interval.
[a] The original mTPI algorithm was "D" for this case and is modified to "S" to collect more information on this dose. The modified decision rule is similar to a 3+3 design.

4. Covariates and Subgroups

4.1 Planned Covariates

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

4.2 Subgroups

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

A safety analysis of CRS outcomes will be performed for subjects who were administered siltuximab in order to assess safety amongst subjects who receive siltuximab due to unavailability of tocilizumab for the treatment of CRS.

5. Definitions

5.1 General Definitions

Age at Enrollment

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

Investigational Product

The term 'investigational product' is used in reference to AMG 330.

Cumulative Dose of AMG 330

AMG 330: The cumulative dose in microgram (µg) is defined as the following with summation over infusions:

$\sum$ (duration of infusion (days) for each dose received × dose received [µg/day])

Bazett-corrected QT Interval (QTcB)

The Bazett correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcB=QT/ (RR/1000)^{1/2}$.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcF=QT/ (RR/1000)^{1/3}$

Derivations of QTcB and QTcF will be performed only when not available.

5.2 Study Points of Reference

Baseline

For any variable, unless otherwise specified, the baseline is the closest value taken prior to, or on the day of, the first administration of AMG 330. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of AMG 330, the baseline value is the value from the screening period measured closest to the day of first administration of AMG 330.

Baseline and Post-baseline ECG Values in Triplicate

The baseline ECG is defined as the mean of all pre-dose assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

For all post-baseline ECG, the mean value for measurements taken at the same assessment will be calculated and used in the analysis.

For pre- and post- dose ECG measurements, unscheduled ECG measurements of a triplicate will be included in the average for a timepoint. Where an ECG is missing within a triplicate, all available data will be averaged for that timepoint.

Change from Baseline

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

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

Percent Change from Baseline

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value)/Baseline Value]x100

5.3 Study Dates

Informed Consent Date

The date on which the subject signs the informed consent form.

Enrollment Date

Enrollment date is defined as the date collected on the Subject Enrollment CRF page.

Study Day 1

Study Day 1 is defined as the first day that AMG 330 is administered to the subject.

Study Day

If date is on or after first administration of AMG 330: study day= (date - date of Study Day 1) + 1

If date is prior to date of first administration of AMG 330: study day= (date – date of Study Day 1)

Last Investigational Product Dose Date

The last IP dose date for each subject is defined as the end date of last infusion of AMG330.

End of Investigational Product (IP) Administration Date

End of IP Administration for each subject is defined as the date of decision was made to end IP reported on the End of IP Administration CRF page.

End of study (EOS)

End of study for an individual subject is defined as the date of the final study visit (EOS visit) when assessments and procedures are performed. The EOS visit should occur approximately 4 weeks (+ 1 week) after the last dose of AMG 330 or prior to the initiation of other AML therapy, whichever occurs earlier. Subjects who complete the EOS visit will be considered to have completed the study.

Death Date

For subjects who die during the study, the death date will be recorded on the end of study CRF in the “date subject ended study” field. Incomplete death dates where only the day of death date is missing will be imputed using the following rules:

Day 1 of the month will be used if year and month indicate that death happened in different month from last known alive date;

One day after last known alive date will be used if death happened in the same month as last known alive date.

The imputed death date will be used in calculation of duration of response, progression-free survival and overall survival.

Last Known Alive Date

For subjects not known to have died, their last date known to be alive will be determined as the latest date associated with clinic visits before data cutoff date including, for example, but not limited to the following:

- Date of Enrollment on Subject Enrollment CRF
- Date First Taken, Date Last Taken on Concomitant Medications CRF
- Date Performed on ECOG Performance Status, Vital Signs, Electrocardiogram, Procedures CRFs
- Admission Date, Discharge Date on Hospitalizations CRF
- Date of Examination on Physical Measurement CRF
- Date Collected on Reproductive Status and Pregnancy Test (Local Lab), Chemistry (Local Lab), Hematology (Local Lab), Coagulation (Local Lab), Urinalysis (local Lab), Immunology (Local lab) CRFs and in central lab data
- Date of Assessment on revised IWG response criteria or modified IWG response criteria for Time Point in CRFs
- Start Date and End Date on Investigational Product Administration CRF
- Date Started and Date Ended or Resulted in Death on Events CRF
- Start date, stop date on Anti-Cancer Therapies, Other Protocol Required Therapy, Other Protocol Required Therapy ([redacted], Dexamethasone), Hematopoietic Stem Cell Transplantation Autologous, Hematopoietic Stem Cell Transplantation Allogenic CRFs
- Subject Status Date if status is Alive on Survival Status CRF
- End of study date if the subject’s primary reason for ending study is not “Lost to follow-up”.

5.4 Endpoints

Treatment-Emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product (enter response based on earliest administration of [redacted], or AMG330, whichever occurred first)" equal to "No" or missing on the Events eCRF and up to 30 days after last administration of AMG330 or end of study date, whichever is earlier. Disease related events (DREs) will be included in the TEAE summary.

The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA. For CRS events, revised grading system will be used as per protocol (Lee et al, 2014).

Treatment-Related AE

A treatment-related AE is any treatment-emergent AE 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 6.2.1.4.

Overall Response:

Overall response definitions are given below for different indications.

Group 1 in dose-escalation cohort / Group 4 (R/R AML)

Response is defined as any of the following:

Complete remission (CR), CR with incomplete recovery (CRi) or morphologic leukemia-free state (MLFS) (all according to Revised International Working Group [IWG] response criteria for AML), or CR with partial hematologic recovery (CRh).

Group 2 (MRD+ AML) (Primary)

Response is defined as CR without minimal residual disease (CRMRD-) or CRi without minimal residual disease (CRiMRD-). MRD- is defined as MRD threshold below 0.1% as per ELN recommendations (Schuurhuis et al., 2018).

Group 2 (MRD+ AML) (Exploratory)

[redacted]

Group 3 (MDS)

Response is defined as any of the following:

CR or marrow CR (all according to Revised IWG response criteria for MDS)

Group 5 and Group 1 in dose-expansion cohort (R/R AML)

Response is defined as any of the following: CRMRD-, CR, CRi, CRh, MLFS, PR.

Minimum Residual Disease (MRD) Response (All groups):

Minimum residual disease response is defined as MRD negative, indicating presence of leukemia cells to 0.1% or lower of white blood cells.

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, disease progression, or death due to any cause, whichever occurs first. Subjects without relapse, disease progression 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.

DOR time in months= earlier of (date of first relapse or disease progression or death or date of censoring) – (date of the first observation of overall response +1)/30.4

Overall Survival (OS)

Overall survival is defined as the time from enrollment until death due to any cause. Subjects alive will be censored at the last known date. 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 date of last contact through the analysis trigger date.

Event-free Survival:

Event-free survival (EFS) is defined as the interval from first administration of AMG 330 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 AMG330. For non-responders, the event date for treatment failure is assigned as the date of first administration of AMG 330.

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 330 +1.

Event-free Survival in months = earlier of (date of treatment failure or relapse or death or date of censoring) – (date of the first administration of AMG 330 +1)/30.4.

Time to Response (TTR)

Time to response defined as the interval from the first administration of AMG 330 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).

6. Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety analysis set defined in Section 6.1.

6.1 Safety Analysis Set

Safety analysis set is defined as all subjects that are enrolled and receive at least 1 dose of AMG 330.

6.2 Dose Limiting Toxicity Evaluable Analysis Set

The DLT-evaluable Analysis Set includes all DLT-evaluable subjects. The analysis of DLT will be restricted to the DLT-evaluable Analysis Set. A subject is not DLT-evaluable if he/she drops out before completion of the DLT window for reasons other than an adverse event related to study drug or the subject has not received IP treatment for at least 14 days at the target dose for a 3- or 4-week cycle or at least 7 days at a target dose for a 2-week cycle. Furthermore, following drug interruptions, if a subject is unable to complete 2 repeat cycles for reasons other than DLT, the subject will not be DLT evaluable.

6.3 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will contain all subjects who have received at least 1 dose of 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) dose decision analyses in the dose-escalation cohorts, (2) interim analyses for safety and preliminary efficacy updates, (3) data analysis prior to public disclosures (e.g. scientific meetings), (4) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (5) the final analysis after all subjects have ended the study.

7.1 Interim Analysis and Early Stopping Guidelines

Interim analyses are planned after all subjects in each indication and each phase have ended the study eg, for R/R AML: all subjects enrolled in Group 1 phase 1a, Groups 4 and 5 have ended the study. Interim analyses may be combined if the analysis timing is close or if the number of subjects in each indication or phase is small. Formal interim analyses will be based on locked database.

Ad-hoc interim analyses for safety and preliminary efficacy updates will be performed. Data analysis prior to public disclosures (e.g. scientific meetings) will also be performed.

Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigators, will review in DLRMs all available cumulative data prior to making dose escalation decisions. For R/R AML (Group 1), dose escalation decisions will be made in accordance with a standard 3+3 design using the rules noted below.

- If no DLT is observed within the DLT window in the initial 3 subjects of a cohort, then dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed within the DLT window in the initial 3 subjects of a cohort, then the cohort will be expanded to 6 subjects. If no further DLT(s) are observed in the 6 subjects, then dose escalation to the next higher dose level cohort will occur. If ≥ 2 subjects experience a DLT in a cohort, then enrollment into this cohort will be stopped.

Ad-hoc interim analyses and DLRM will be based on as-is snapshot with routine data cleaning. Database will not be locked for these analyses.

Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose level with an observed incidence of DLT in < 33% of subjects enrolled in a cohort dose level. At least 6 evaluable subjects will be treated at the MTD or highest tested dose.

The mTPI-2 model will be used to make dosing recommendations for Group 2 and Group 3 (see section 3.3 for details). 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.

Enrollment of a cohort can be suspended at any time based on safety findings at any dose level and in the expansion cohort, if at any time ≥ 33% of subjects treated at the MTD (including those treated at the MTD in the expansion phase) or RP2D experience a DLT within the DLT window, and a DLRM will be convened. In addition, the study may be discontinued or modified at any time due to documented safety findings.

Dose Level Review Team (DLRT)

For each group, DLRMs will be held to review data, monitor safety, and make recommendations 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, global safety officer or designee, clinical study manager, biostatistician, PK scientist (optional), and other functional area representatives as appropriate. A quorum as defined below must be in attendance for the DLRM. The quorum is defined as > 50% of the participating investigators 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 required voting members of the DLRT include: investigators, Amgen medical monitor, early development leader, and global safety officer or designee.

The following recommendations can be made by the DLRT:

- dose escalation / de-escalation decisions
- expansion of a cohort
- continuation, delay or termination of dosing
- implementation of dose step(s)
- extension of the run-in phase in case of dose step(s)
- extension of the duration of treatment cycles
- implementation of mandatory steroid pre-treatment in case of cytokine release syndrome-related adverse events
- enrollment of additional subjects in the expansion cohort
- duration of the DLT period based on emergent safety data

- level and duration of dose steps (schedule) adjustment based on safety, and available PK and PD data

All available study data, 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 recommendations. Data will not need to be source data verified and queries will not need to be resolved prior to the DLRM.

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

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT once the first 5 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment / study, whichever occurs earlier. Once the first 10 subjects have at least completed their first treatment cycle plus two weeks or dropped out of study, all available study data will be reviewed by the DLRT. If there is at least 1 responding subject within these first 10 subjects, the DLRT will determine if an additional (up to 20) subjects may be enrolled. If additional subjects are enrolled after the first 10 subjects, all available study data will be reviewed (with recruitment ongoing) by the DLRT after every 5 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment / study. Ad hoc meetings may be convened any time in case of important safety events

7.2 Primary Analysis

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or terminated the study early. Primary analysis will be based on locked database to prevent further changes.

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 approximately 6 months after enrollment of the last study subject. Final analysis will be based on locked database to prevent further changes.

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

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. Details of PK, Antibody, and external lab data transfer to the database will be outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP. 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 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.

- 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.
- PD concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PD 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

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 CPMS practices. All excluded observations will be detailed by CPMS along with reasons for exclusion, in accordance with standard CPMS practices.

Pharmacodynamic (PD) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PD evaluation practice. Descriptive statistics will be used to identify potential outliers in key variables.

Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

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 demographic, safety, PK, PD and biomarker data by dose, dose schedule, time as appropriate, and each indication (Group1, Group2, Group3) separately. Unless otherwise stated, the data analysis will be conducted using subjects in the Safety Analysis Set. 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. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Data listings will include all available data from all enrolled subjects unless specified otherwise. Additional analysis for Group 4 and Group 5 will be specified in SSAP.

Data analysis will occur at the following time points:

- Interim analyses as described in Section 7.1.
- The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or terminated the study early.

- A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study.

Confidence intervals 80% and 95% (CI) for proportions will be estimated using an exact method proposed by Clopper and Pearson, 1934.

9.2 Subject Accountability

A summary of subject disposition with discontinuation reasons, and AMG 330 completion and discontinuation will be provided. Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

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 course of the study. Eligibility deviations are defined in the protocol. A subject listing and summary table will be provided for Important Protocol Deviations.

9.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristic will be summarized 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.

The baseline characteristics to be summarized include:

Demographic

- Sex: Male, Female
- Age: 18-64, 65-74, 75-84, >=85
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino

Baseline characteristics for R/R AML

- Height
- Weight
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Type of AML (at initial diagnosis and at study entry)
- Prior lines of therapies

- Responses to the prior lines of therapies
- Prior hematopoietic stem cell transplant
- Disease duration
- Bone marrow blast
- Baseline Tumor Burden
- ELN risk classification (at initial diagnosis and at study entry)
- White blood cells
- Absolute Neutrophil count
- Platelet count

Baseline characteristics for MRD

- Height
- Weight
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Type of AML (at initial diagnosis and at study entry)
- MRD status
- Prior lines of therapies
- Responses to the prior lines of therapies
- Prior hematopoietic stem cell transplant
- Disease duration
- Bone marrow blast
- Baseline Tumor Burden
- White blood cells
- Absolute Neutrophil count
- Platelet count

Baseline characteristics for MDS

- Height
- Weight
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Type of MDS (at initial diagnosis and at study entry)
- MDS Risk(IPSS-R) (at initial diagnosis and at study entry)

- MDS status at study entry
- Prior lines of therapies
- Responses to the prior lines of therapies
- Prior hematopoietic stem cell transplant
- Disease duration
- Bone marrow blast
- Baseline Tumor Burden
- White blood cells
- Absolute Neutrophil count
- Platelet count

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint(s)

No efficacy parameter is considered in primary endpoints

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The proportion of subjects with an overall response (Section 5.4) with corresponding exact 80% and 95% Confidence Intervals will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by cohort. The proportion of subjects who are event-free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method. The proportion of subjects with MRD response at the 0.1% threshold and the 0.01% threshold amongst subjects in the Safety Analysis Set will be summarized by cohort.

Listings indicating time to response, duration of response (DOR), and event-free survival will be produced for responders for each indication separately. For subjects in dose expansion cohorts, Kaplan Meier curves may be presented for event-free survival and overall survival with estimates for rates and 80% CI at selected weeks. DOR and time to response will only be analyzed for subjects who achieved an overall response.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The following statistical analyses will be considered exploratory and will be performed by clinical biomarker group in Department of Translational Medicine only when deemed appropriate. Relationships between changes in tumor dynamics and above biomarkers of interest listed as exploratory endpoints will be explored. Changes in expression levels of biomarkers and their relationship to dose may also be explored. Summary statistics over time will be provided and graphical presentations may be used. The relationship between

AMG 330 exposure and PD effects and related biomarkers in blood, or tumor specimens and/or AMG 330 exposure and clinical outcomes (eg, tumor response) will be also explored if deemed appropriate. Details of analysis will be provided in a Contributing Scientific Report for exploratory biomarker analysis. Pharmacodynamic (PD) biomarkers for AMG 330 mechanism of action (Depletion of LSCs, Lymphocyte counts, CD33+ monocytes ,T cells, T cell activation (including T cell subsets), Other immune subsets, [redacted].

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 330. Unless otherwise noted, treatment groups will be defined based on the planned doses for Cycle 1.

9.6.2 Analyses of Dose Limiting Toxicities

The analysis of Dose limiting toxicities (DLT) will be based on the DLT Evaluable Analysis Set. A listing and summary of the subject incidence of dose limiting toxicities (DLT) will be provided.

9.6.3 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

The subject incidence of adverse events (including disease related events) will be summarized for all treatment-emergent adverse events, 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 grade. In addition, SAEs and grade 3 and above adverse events will be summarized by preferred term in descending order of frequency.

The severity of each adverse event will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria with the exception of cytokine release

syndrome (CRS), which will be graded using the criteria referenced in the publication by Lee et al (2014).

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term and worst grade. CRS will be summarized by grade and symptom.

TEAE summaries will be provided both by cohort and by overall groups.

9.6.4 Laboratory Test Results

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

In interim, primary and final analyses, depending on the size and scope of changes in selected laboratory data, summaries of selected laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided. Unscheduled assessments will be included in these summaries.

9.6.5 Vital Signs

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

In interim, primary and final analyses, depending on the size and scope of changes, summaries of vital signs (resting systolic/diastolic blood pressure, heart rate, respirations and temperature) data over time and/or changes from baseline over time may be provided. Unscheduled assessments will be included in these summaries.

9.6.6 Physical Measurements

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

9.6.7 Electrocardiogram

All on-study electrocardiogram (ECG) data (QRS, QT, QTc, RR, and PR intervals) will be listed.

Where multiple 12-lead ECG measurements are taken at the same assessment (they are planned to be recorded in triplicate <30 seconds apart) the mean value will be calculated and used in the analysis. Their primary approach will include all measurements taken at the assessment for the derivation of the mean value. The baseline ECG is defined as the

mean of all pre-dose assessments; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages.

In the event of extreme outlier readings, an additional sensitivity analysis will be conducted where the outlier measurement is excluded from the derivation of the mean for that assessment. The criteria used to define an outlier measurement will be determined based upon inspection of the data.

For pre- and post- dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate will be included in the average for a time point. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Summaries over time and/or changes from baseline over time will be provided for all 12-lead ECG parameters. The analysis of Fridericia's (QTcF) QT correction and Bazett's (QTcB) QT correction will be performed.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcF and QTcB. 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. A listing of the subjects with > 60 msec change from baseline in QTcF and QTcB will be provided.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF and QTcB. 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. A listing of the subjects with > 500 msec post baseline in QTcF and QTcB will be provided.

9.6.8 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 330 antibodies (binding) at any time by cohorts and indication (Group1, Group2, Group3) will be tabulated. Positive anti-AMG 330 antibody data will be listed and reviewed for each subject. The impact of immunogenicity on safety may be explored by assessing adverse events and serious adverse events.

9.6.9 Exposure to Investigational Product

Details of AMG 330 administration will be listed for every subject for DLRM. In primary and final analyses, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided. Descriptive statistics will be produced to describe the number of cycles initiated, completed and discontinued, the duration of therapy and the cumulative dose will be produced to describe the exposure to investigational product by groups and dose cohorts separately.

9.6.10 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. A subject listing of all concomitant medications will be presented for DLRM. In the interim, primary and final analyses, the number and proportion of subjects receiving concomitant medications will be summarized by preferred term for each treatment group and indication as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

For AMG 330, pharmacokinetic parameters half-life, steady-state concentration, volume of distribution, and clearance) will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 330 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

Serum concentrations of AMG 330 will be determined using a validated assay. Parameters to characterize cellular kinetics related to cell expansion (eg, C_{max}, T_{max} and partial AUC) and cell persistence (eg, $T_{1/2}$, T_{last} and C_{last}) in PBMCs, 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 cellular kinetic 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 Cellular kinetic analyses, including but not limited to analysis of the relationship between AMG 330 dose and exposure parameters (AUC and Cmax) and dose proportionality assessments, may also be conducted. Based on the review of the data, analyses to describe the relationship between AMG 330 exposure and either Pharmacodynamic effect and/or clinical outcome may also be performed.

A preliminary assessment of dose proportionality will be made using the Power Model Statistical analysis of $AUC_{(0\text{-}t)}$ and Cmax of AMG 330 will be performed after log transformation of the data. The Power Model:

$Y = \alpha \, dose^{\beta}$

where Y is the pharmacokinetic parameter and α is an intercept term. This becomes a linear relationship following a logarithmic transformation, to which a linear regression approach can be applied as,

$log(Y) = \beta \times log\,(dose) + log(\alpha)$

The coefficient of the slope with 90% confidence intervals, on the log scale, will be calculated.

Descriptive statistics will be provided for biomarker data by dose, dose schedule, and time as appropriate.

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

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers will be considered exploratory and may be performed after collection of all samples during the conduct of the study and therefore may

be reported after the primary analysis. Changes in expression or expansion level of biomarkers and their relationship to dose may be evaluated. Summary statistics over time may be provided and graphical presentations may be used. Details of analysis will be provided in Contributing Scientific Report for exploratory biomarker analysis.

10. Changes From Protocol-specified Analyses

- The following inclusions in the SAP are in anticipation of incorporation in Protocol Amendment 10:
    - event-free survival endpoints replacing time to progression in R/R AML and MDS groups to address relapse/refractory AML subjects who are already in a progressive state and never respond.
    - removal of duration of response endpoint for MRD+ AML group
    - overall survival for all groups in the expansion cohort
    - Treatment-emergent definition accounts for long-term follow-up by defining events as treatment-emergent by looking up to the earlier of 30 days after last dose of AMG 330 or end of study date.
    - Summary of adverse events amongst subjects who take siltuximab.

11. Literature Citations / References

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

12. Prioritization of Analyses

NA

13. Data Not Covered by This Plan

NA

14. Appendices

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

Imputation Rules for Partial or Missing Dates for Adverse Events and Concomitant Medications

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

If a death date is totally missing:

Do not impute and censor the subject survival time.

Appendix C. Summary of Changes

Protocol Title:

Replace:

A Phase 1 First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 330 Administered as Continuous Intravenous Infusion in Subjects With Relapsed/Refractory Acute Myeloid Leukemia.

With:

A Phase 1 First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of AMG 330 Administered as Continuous Intravenous Infusion in Subjects with Myeloid Malignancies.

Section: Objectives, Endpoints and Hypotheses, Hypotheses and/or Estimation

Primary Objectives:

Replace:

- Evaluate the safety and tolerability of AMG 330 in adult subjects with relapsed/refractory Acute Myeloid Leukemia (AML)
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)]

With:

- Evaluate the safety and tolerability of AMG 330 in adult subjects with relapsed/refractory AML, MRD+ AML and MDS
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose [eg, recommended phase 2 dose (RP2D)] of AMG 330 in adult with relapsed/refractory AML, MRD+AML and MDS

Secondary Objectives:

Replace:

- the duration of response and time to response and time to progression

With:

- the duration of response, event-free survival, time to response, and overall survival

Added:

- the number and proportion of subjects with MDS who respond to treatment with AMG 330. Response is defined as any of the following: CR or marrow CR (all according to Revised IWG response criteria).
- the number and proportion of subjects with MRD-positive AML (Group 2) who respond to treatment with AMG 330. Response is defined as conversion from MRD+ status with 0.1% threshold to MRD- status.

Exploratory Objectives:

Added:

- Evaluate the effect of [redacted] premedication and alternative dosing schedules on the safety and tolerability of AMG 330 in adult subjects with relapsed/refractory AML
- Explore the additional thresholds of conversions to MRD- status in MRD+ AML subjects as an efficacy measure for AMG 330 treatment

Deleted:

- Evaluate potential effect of AMG 330-mediated cytokine elevation on hepatic CYP3A activity.

Primary Endpoint:

Replace:

- Safety: subject incidence and grade of adverse events and DLTs.

With:

- Safety: subject incidence and grade of adverse events (AEs) and dose limiting toxicities (DLTs).

Secondary Endpoints:

Replace:

- Incidence of anti-AMG 330 antibody formation.
- Efficacy parameters: response (response defined as CR, CRi, morphologic leukemia-free state [per modified IWG criteria] or CRh*), time to progression, duration of response, time to response.

With:

- Anti-AMG 330 antibody formation
- Efficacy parameters for R/R AML: response (response defined as CR/CRi/morphologic leukemia-free state [per modified IWG criteria] or CRh), duration of response, time to response, event-free survival and overall survival (duration of response, event-free survival, and overall survival will only be measured in the expansion cohort).

Added:

- Efficacy parameters for MRD-positive AML: response rate (response defined as conversion from MRD+ status with 0.1% threshold to MRD-), time to response, relapse-free survival, and overall survival (relapse-free survival and overall survival will only be measured in the expansion cohort)
- Efficacy parameters for MDS: response (response defined as CR or marrow complete remission [per International Working Group (IWG) standardized response criteria]), duration of response, event-free survival, time to response, event-free survival and overall survival (duration of response, event-free survival, and overall survival will only be measured in the expansion cohort)

Exploratory Endpoints:

Replace:

- Lymphocyte counts, CD33+ monocytes and T cells, as well as T cell activation (including T cell subsets).

With:

- Lymphocyte counts, cluster of differentiation (CD) 33+ monocytes and T cells, as well as T cell activation (including T cell subsets). Other immune subsets may also be examined.

Added:

- [redacted]
- [redacted]
- Frequency and severity of cytokine release syndrome (CRS) and other AEs following [redacted] premedication, and alternative dose step schedules of AMG330 [redacted]

Deleted:

- Quantification of CYP3A enzyme activity with markers (eg, plasma levels of 4β-hydroxycholesterol, urinary 6β-hydroxycortisol/cortisol ratio level, CYP3A5*3 genotype etc.)

Hypotheses and/or Estimations:

Replace:

AMG 330 will demonstrate evidence of anti-leukemic activity at a well-tolerated dose in subjects with AML.

With:

AMG 330 will demonstrate evidence of anti-leukemic activity at a well-tolerated dose in subjects with AML and MDS.

Section: Study Overview, Study Design, Sample Size, Adaptive Design
Replace:

Study Design:

This is a first in human, open-label, phase 1 sequential dose escalation study. AMG 330 will be evaluated as a continuous intravenous (cIV) infusion in adult subjects with relapsed/refractory AML.

The dose-escalation cohorts will estimate the MTD, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 330. Planned dose levels for the dose-escalation cohorts are as follows: 0.5, [redacted], and 960 µg/day.

It is anticipated that two MTDs may be estimated, one for the initial dosing and one for the subsequent dosing. Each MTD will be estimated following 3+3 decision rules. Intermediate dose level(s) may be evaluated as necessary. In the event that one subject experiences

a DLT, then the dose administered for successive cohorts will escalate by no more than 50% (ie, a dose increment of no more than 1.5 times the previous dose) after discussion at the Dose Level Review Meeting (DLRM).

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 330.

With:

Study Design:

This is a first-in-human, open-label, phase 1 sequential dose escalation study. AMG 330 will be evaluated as a continuous intravenous (cIV) infusion in adult subjects with relapsed/refractory (R/R) AML (Group 1), MRD+ AML (Group 2) and MDS (Group 3). The study will be conducted at approximately 17 sites in Germany, the Netherlands, Japan, the United States and Canada.

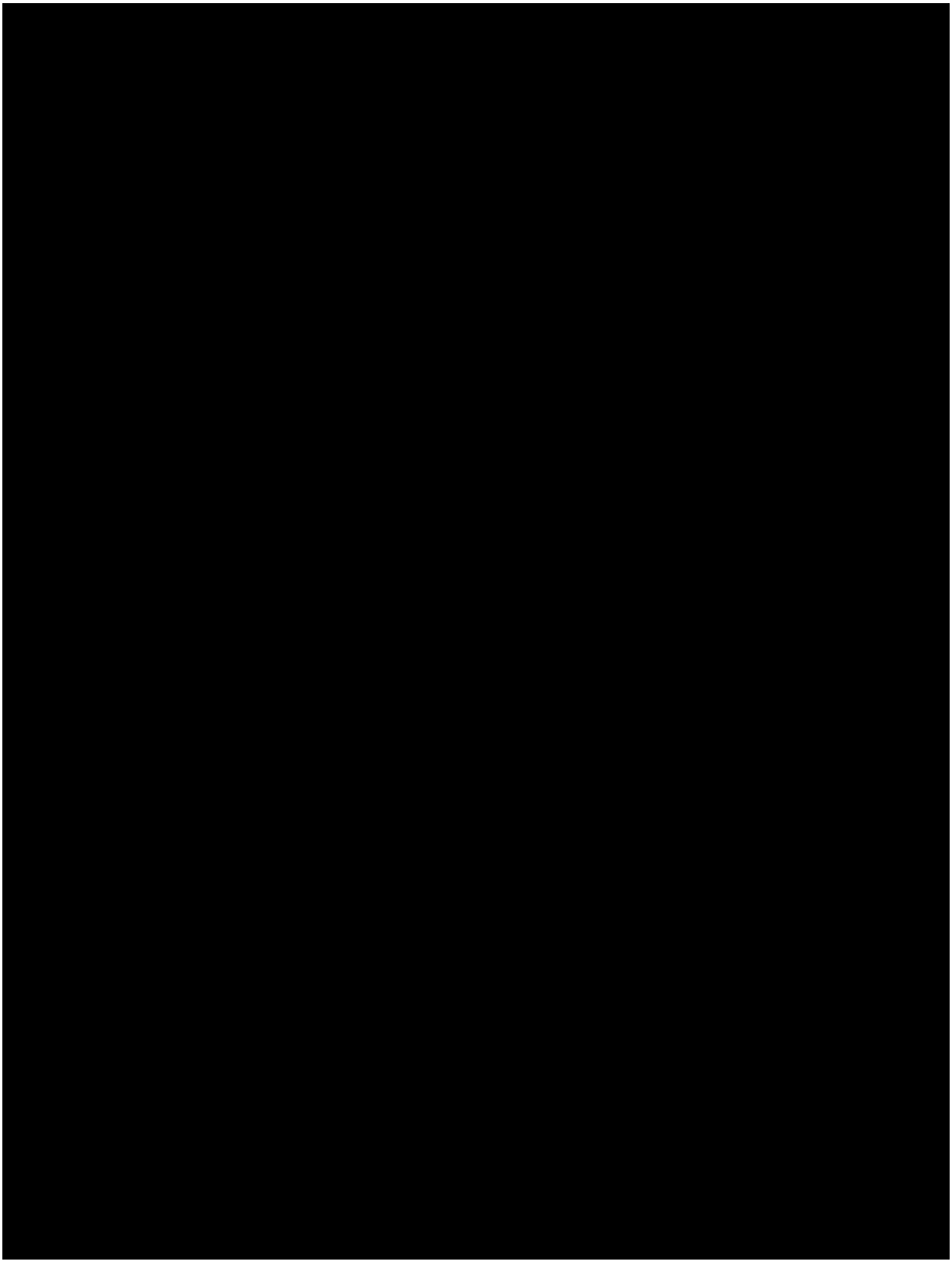
The dose-escalation cohorts will estimate the MTD/biologically active dose, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 330.

For R/R AML (Group 1), planned dose levels for the dose-escalation cohorts are as follows: 0.5, [redacted] and 960 µg/day. Intermediate and/or higher dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary to reach MTD. The same dose level may be tested in multiple cohorts, but with different dose steps and/or different cycle lengths.

For MRD+ AML (Group 2), planned dose levels for the dose-escalation cohorts are as follows: [redacted] and 960 µg/day. Each target dose level will be preceded by dose steps and additional dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary. Escalation can continue until MTD for MDS is established. Selected target dose levels, with the exception of the maximal tested dose, that have been deemed safe in subjects with R/R AML (Group 1) could be skipped in Group 3 phase 1a dose escalation cohorts based on available safety, PK, and PD data if recommended by the DLRT.

It is anticipated that more than one MTD may be estimated, one for each dose step and one for the target dose. Should the initial dose be limited by adverse events related to first dose effects (eg, cytokine release syndrome [CRS]), the second MTD for the target dose will be estimated after giving the initial dose at MTD (dose step). Starting with cohort 6 (R/R AML, Group 1), a dose step in each cycle is mandatory for all newly enrolled subjects. Administration of a prophylactic steroid dose (8 mg IV dexamethasone) within 1

hour prior to the dose step for prevention of cytokine release is mandatory. The additional assessments described in the schedule of assessments for dose steps (in Protocol Table 14) apply.



[redacted]

For MDS (Group 3), planned dose levels for dose-escalation cohorts are as follows: [redacted] and 960 µg/day. Each target dose will be preceded by dose steps. Intermediate dose steps and additional dose level(s) up to 1.6 mg of AMG 330 may be evaluated as necessary. Escalation can continue until MTD for MDS is established.

It is anticipated that more than one MTD may be estimated, one for each dose step and one for the target dose. Should the initial dose be limited by adverse events related to first dose effects (eg, cytokine release syndrome [CRS]), the second MTD for the target dose will be estimated after giving the initial dose at MTD (dose step). Starting with cohort 6 (R/R AML, Group 1), a dose step in each cycle is mandatory for all newly enrolled subjects. Administration of a prophylactic steroid dose (8 mg IV dexamethasone) within 1 hour prior to the dose step for prevention of cytokine release is mandatory. The additional assessments described in the schedule of assessments for dose steps (in Protocol Table 14) apply.

[redacted]

[redacted]

Replace:

Dose Escalation:

For both MTDs (initial and target dose), dose escalation will estimate the MTD. The estimated MTD is defined as the maximum dose at which fewer than one-third of subjects experience as dose limiting toxicity (DLT) (minimum of 6 evaluable subjects). Dose Escalation will be conducted in two stages. In the single subject cohorts, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events

will be observed. Once higher dose levels are open for enrollment or when drug related safety or efficacy signals are observed, the 3+3 design will be triggered.

The starting dose and dose level schema is shown below in Table.

Single Subject Cohorts:

In the initial dose escalation cohorts, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active. AMG 330 will initially be administered at escalating doses in a 2 weeks on / 1-4 weeks off schedule. This schedule may be modified by DLRT decision (see section 6.2.1.1 of protocol for details).

The 3+3 design will be triggered if at least 1 subject experiences any of the

following drug related safety or efficacy signals (whichever is earlier):

- Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 adverse events other than thrombocytopenia, anemia, or neutropenia
- DLT
- Objective response

Multiple Subject Cohorts (3+3 Dose Level Decision Rules):

It is anticipated that up to 8 additional cohorts will be enrolled using a standard 3+3 design. Each cohort will enroll up to 6 evaluable subjects. There will be at least a 96-hour interval between the start of treatment of the first and second subject in each cohort. Communication of safety data (clinical, basic laboratory and vital signs) to the sponsor

and other sites will occur during this period as needed before dosing other subjects. In addition, there will be at least a 96-hour interval between the start of treatment of the second subject and all subsequent subjects in each cohort. Following this, no more than 3 subjects should be enrolled in two weeks. Enrollment number decision rules for any given dose level cohort are shown in the table below.

3+3 Dose Level Decision Rules

#Subjects[a]	#Subjects with DLT	Decision
3	1	Enroll 3 additional subjects same dose level
3	0	Escalate[b]
3	≥ 2	De-escalate[c]
6	1	Escalate[b]
6	≥ 2	De-escalate[c]

[a] Subejcts who are not DLT-evaluable are excluded from the count of subjects enrolled
[b] If final dose level has been reached, accrual will be suspended.
[c] If 6 subjects already entered at next lower dose level, the estimated MTD has been established.

For each DLRM (refer to Appendix D), the DLRT will determine the values for dose escalation/de-escalation as well as determine the appropriateness of the upcoming 3+3 decision rules.

DLRT may select the proposed recommended phase 2 dose(s) (RP2D) even when the MTD is not yet reached. Once the proposed RP2D is identified, AMG 330 will be evaluated in expansion cohorts for each of the selected tumor subtypes.

With:

Dose Escalation:

For Group 1 (R/R AML), dose escalation will be conducted in two stages. In the single subject cohorts, single subjects will be enrolled at dose levels anticipated to be lower than those at which adverse events related to AMG 330 will be observed. Once higher dose levels are open for enrollment or drug related safety or efficacy signals are observed, multiple subject cohorts of up to 6 subjects per dose level will open for enrollment (3+3 design). Subjects who complete the DLT period may proceed to a higher dose level for the following treatment cycle if no DLT has been reported for either this subject or any other subject in this dose cohort after completion of the DLT period, and once the next dose cohort is open for enrollment. (see Section 7.2.2 in protocol for details on assessments applicable in case of intra-subject dose escalation).

In Group 1 (R/R AML), should the initial dose be limited by adverse events related to first dose effects (eg, CRS), dose steps will be implemented. An optimal dose step schedule and MTD for the target dose will be estimated following decision rules.

For Groups 2 and 3 (MRD+ AML and MDS), each dose escalation cohort will enroll a minimum of 3 to a maximum of 9 evaluable subjects. Dose escalation will be guided by a modified toxicity probability interval approach (mTPI-2; Guo et al, 2017). The DLRT will review all available safety, laboratory, PK and PD data and provide dose-finding recommendations.

For Groups 1, 2 and 3, enrollment will occur simultaneously, and each Group will progress from the dose escalation to the dose expansion independently. The total number of subjects to be enrolled for the dose escalation will depend on the toxicities observed as the study progresses. Additional subjects may be required if other dose levels or alternate treatment schedules are explored.

Enrollment in Group 4 is independent from enrollment in Groups 1, 2 and 3. For Group 4, enrollment in Arm 1 will occur first. Once all subjects in Arm 1 have initiated treatment, enrollment into Arm 2 will begin. Once all Group 4 subjects have completed the DLT period, enrollment into Group 5 can commence. If there are 2 arms in Group 5, all subjects in Arm 1 must have initiated treatment before enrollment into Arm 2 can begin.

Replace:

Expansion Cohort:

The objective of dose expansion is to get further safety and efficacy data in subjects. 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 330.

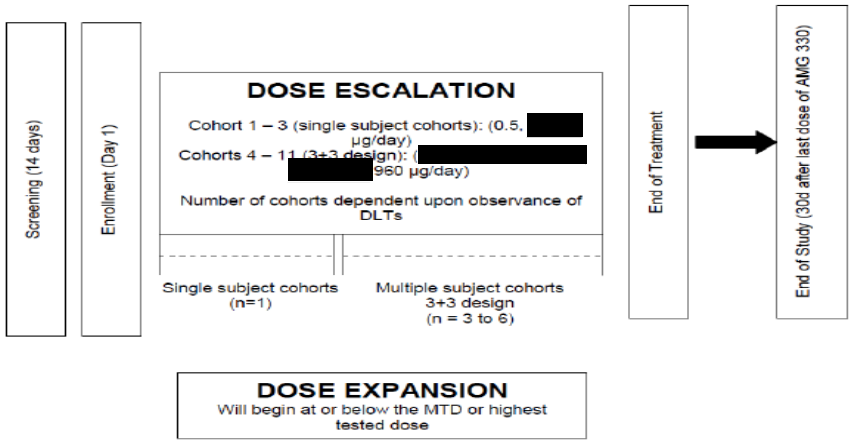
The dose or doses to be evaluated in the expansion phase will be based on results from the dose escalation phase. Subjects may be enrolled continuously (ie, without waiting for Cycle 1 completion of patients who have received the first dose) unless there is a more than 33% incidence of DLTs at any given time. After 10 subjects enroll in the expansion cohorts, TPI Bayesian model will be used to re-challenge the MTD concluded in dose escalation phase. The subsequent subjects to be enrolled in dose expansion may be dosed with the updated dose level, determined by the DLRT. Once all subjects are enrolled in expansion cohort and complete the DLT window, a final estimation of the RP2D

will be made based on the TPI Bayesian model utilizing all DLT-evaluable subjects from the dose escalation and dose expansion.

3.1.1 Study Schema

The overall study design is described by a study schema at the end of the protocol synopsis and below (Figure 1).

Figure 1. Study Design and Treatment Scheme



With:

Expansion Cohort:

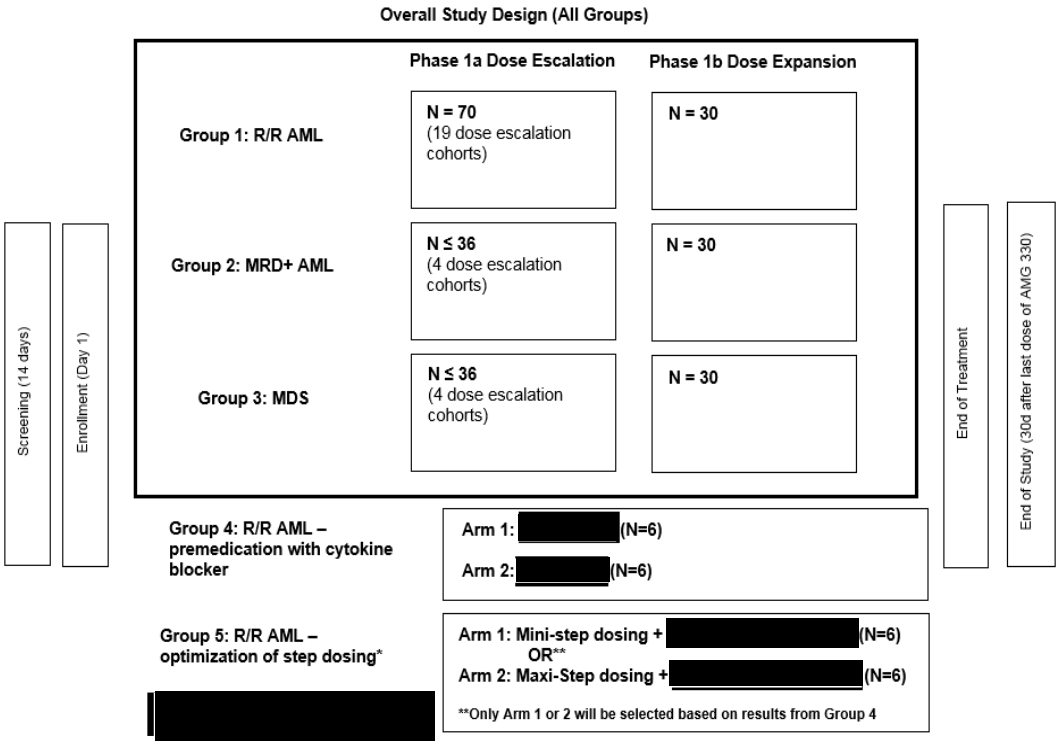
At completion of the dose escalation cohorts, additional subjects will be enrolled in dose expansion cohorts to gain further clinical experience, safety and efficacy data in subjects with AMG 330. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts. If there is at least 1 responding subject in the first 10 subjects enrolled in expansion cohort, additional (up to 20) subjects will be enrolled after evaluating safety, tolerability and anti-leukemia activity of AMG 330 using all available cumulative data. Additional expansion cohorts testing alternative dose levels or biologic subsets may be considered by amendment.

For each Group, a final estimate of the MTD and/or RP2D will be evaluated and confirmed utilizing all DLT-evaluable subjects from the dose escalation and the dose expansion cohorts.

Study Schema:

The overall study design is described by a study schema at the end of the protocol synopsis and below (Figure 1).

Figure 1. Study Design and Treatment Scheme



Replace:

Sample Size:

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.

The sample size in the dose escalation is based on practical considerations and it is consistent with conventional oncology studies with the objective to estimate the MTD. With 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 6 subjects per cohort, there is a 47-91% 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% response rate, the expected 80% CI would be 5.5% to 45.0% with the half-width 19.8%.

With:

Sample Size:

[redacted]

Added:

Adaptive Design:

For MRD+ AML (Group 2) and MDS (Group 3), dose exploration will be guided by pre-specified monitoring rules, which is based on a modified toxicity probability interval

algorithm (mTPI-2; Guo et al, 2017) with a target DLT rate of 25% and an acceptable toxicity probability interval of 20%-30%. Consistent with conventional oncology phase 1 study designs (eg, 3 + 3 design) and given the imprecision with making decisions using as few as 3 subjects, in the instance of 1 DLT in the initial 3 subjects at a dose level then, as appropriate, the design allows expansion at the dose level beyond 3 subjects.

The mTPI-2 algorithm employs a simple beta-binomial Bayesian model. Let pT be the target toxicity level and (pT − ϵ1, pT + ϵ2) be the equivalence toxicity interval denoted as EI. The unit toxicity interval (0, 1) is divided into subintervals with equal length given by (ϵ1 + ϵ2). Let the under-dosing intervals (LI) denote for a set of intervals below EI, and the overdosing intervals (HI) for a set of intervals above EI. The 3 types of dosing intervals (EI, LI, HI) are associated with 3 different dose escalation decisions. The LI correspond to a dose escalation (E), the HI correspond to a dose de-escalation (D), and proper dosing intervals (EI) correspond to staying at the current dose (S). This study design uses a target toxicity level, pT of 25%, and EI of (20%, 30%).

Decision rules are based on the unit probability mass (UPM) calculated on these equal-length intervals. Given an interval and a probability distribution, the UPM of that interval is defined as the probability of the interval divided by the length of the interval. The mTPI-2 design calculates the UPMs for the each of equal-length dosing intervals. If the interval with the largest UPM is from LI, EI or HI, then the corresponding dose decision would be E, S, or D, respectively.

A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT rate pT (ie, P [DLT > p_T | data] > 95%) with at least 3 evaluable subjects treated and evaluated at that dose level.

After the escalation phase is completed, final DLT rates at each dose level will be estimated by isotonic regression (Ji et al, 2010). The MTD will be determined as the dose level with the DLT estimate closest to the target toxicity level of 25%. In the case of dose levels with estimated toxicity of equal distance (tied dose levels) from the target toxicity of 25%, the following approach will be used (Ji et al, 2010): among all tied dose levels the highest dose level with target toxicity ≤ 25% will be selected, unless all tied dose levels have estimated toxicity >25%, in which case the lowest dose level will be selected.

mTPI-2 Trial Monitoring Table

Number of DLTs	n=3	n=4	n=5	n=6	n=7	n=8	n=9
0	E	E	E	E	E	E	E
1	S[a]	S	S	E	E	E	E
2	D	D	D	D	S	S	E
3	DU	DU	DU	D	D	D	D
4	.	DU	DU	DU	DU	DU	D
5	.	.	DU	DU	DU	DU	DU
6	.	.	.	DU	DU	DU	DU
7	.	.	.	.	DU	DU	DU
8	.	.	.	.	.	DU	DU
9	.	.	.	.	.	.	DU

DLT = dose-limiting toxicity; E = escalate to the next higher dose level; S = stay at the current dose level; D = de-escalate to the next lower dose level; DU = current dose is unacceptably toxic; mTPI = modified toxicity probability interval.
[a] The original mTPI algorithm was "D" for this case and is modified to "S" to collect more information on this dose. The modified decision rule is similar to a 3+3 design.

Section: Covariates and Subgroups, Definitions

Added:

Planned Covariates:

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

Subgroups:

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoints.

[redacted].

Definitions:

General Definitions

Added:

Investigational Product

The term 'investigational product' is used in reference to AMG 330.

Cumulative Dose of AMG 330

AMG 330: The cumulative dose in microgram (µg) is defined as the following with summation over infusions:

$\sum$ (duration of infusion (days) for each dose received × dose received [µg/day])

Study Points of Reference

Replace:

Change from Baseline

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

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

Change (percent) from Baseline=[(Post-baseline Value – Baseline Value)/Baseline Value]x100

With:

Change from Baseline

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

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

Percent Change from Baseline

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value)/Baseline Value]x100

Study Dates

Replace:

Enrollment Date

Enrollment date is defined as the enrolled on day 1 (cycle 1 day 1) when the cIV infusion with investigational product (AMG 330) is started.

Study Day

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

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

Study Day 1

It is defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject.

With:

Enrollment Date

Enrollment date is defined as the date collected on the Subject Enrollment CRF page.

Study Day

If date is on or after first administration of AMG 330: study day= (date - date of Study Day 1) + 1

If date is prior to date of first administration of AMG 330: study day= (date – date of Study Day 1)

Study Day 1

Study Day 1 is defined as the first day that AMG 330 is administered to the subject.

Added:

Informed Consent Date

The date on which the subject signs the informed consent form.

End of Investigational Product (IP) Administration Date

End of IP Administration for each subject is defined as the date of decision was made to end IP reported on the End of IP Administration CRF page.

End of study (EOS)

End of study for an individual subject is defined as the date of the final study visit (EOS visit) when assessments and procedures are performed. The EOS visit should occur approximately 4 weeks (+ 1 week) after the last dose of AMG 330 or prior to the initiation of other AML therapy, whichever occurs earlier. Subjects who complete the EOS visit will be considered to have completed the study.

Death Date

For subjects who die during the study, the death date will be recorded on the end of study CRF in the “date subject ended study” field. Incomplete death dates where only the day of death date is missing will be imputed using the following rules:

Day 1 of the month will be used if year and month indicate that death happened in different month from last known alive date;

One day after last known alive date will be used if death happened in the same month as last known alive date.

The imputed death date will be used in calculation of duration of response, progression-free survival and overall survival.

Last Known Alive Date

For subjects not known to have died, their last date known to be alive will be determined as the latest date associated with clinic visits before data cutoff date including, for example, but not limited to the following:

- Date of Enrollment on Subject Enrollment CRF
- Date First Taken, Date Last Taken on Concomitant Medications CRF

- Date Performed on ECOG Performance Status, Vital Signs, Electrocardiogram, Procedures CRFs
- Admission Date, Discharge Date on Hospitalizations CRF
- Date of Examination on Physical Measurement CRF
- Date Collected on Reproductive Status and Pregnancy Test (Local Lab), Chemistry (Local Lab), Hematology (Local Lab), Coagulation (Local Lab), Urinalysis (local Lab), Immunology (Local lab) CRFs and in central lab data
- Date of Assessment on revised IWG response criteria or modified IWG response criteria for Time Point in CRFs
- Start Date and End Date on Investigational Product Administration CRF
- Date Started and Date Ended or Resulted in Death on Events CRF
- Start date, stop date on Anti-Cancer Therapies, Other Protocol Required Therapy, Other Protocol Required Therapy ([redacted], Dexamethasone), Hematopoietic Stem Cell Transplantation Autologous, Hematopoietic Stem Cell Transplantation Allogenic CRFs
- Subject Status Date if status is Alive on Survival Status CRF
- End of study date if the subject's primary reason for ending study is not "Lost to follow-up".

Endpoints

Replace:

Treatment-Emergent Adverse Event (TEAE)

An adverse event that occurs or worsens on or after the first administration of protocol specified treatment or within 30 days after the last dose of protocol-specified therapy. The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA.

Duration of Response (DOR)

Duration of response is defined as the number of days between the date of the first tumor assessment indicating an overall response through to the subsequent date of progression as classified by modified irRC 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 radiological 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*).

Dose Limiting Toxicities (DLT):

A DLT will be defined as any grade ≥ 3 adverse event occurring during a DLT window, and regarded by the investigator and/or sponsor to be related to AMG 330.

With:

Treatment-Emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product (AMG 330)" equal to "No" or missing on the Events eCRF and up to the End of Study date. Disease related events (DREs) will be included in the TEAE summary.

The severity of each adverse event will be graded using the CTCAE version 4.0. Adverse events will be coded using MedDRA. For CRS events, revised grading system will be used as per protocol (Lee et al, 2014).

Duration of Response (DOR)

Duration of response is defined as the interval from the date of the first disease assessment indicating an objective response to the first documented relapse, disease progression, or death due to any cause, whichever occurs first. Subjects without relapse, disease progression 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: (date of first relapse or disease progression or death or date of censoring – date of the first observation of overall response +1).

DOR time in months: (date of first relapse or disease progression or death or date of censoring – date of the first observation of overall response +1)/30.4

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 6.2.1.4.

Added:

Treatment-Related AE

A treatment-related AE is any treatment-emergent AE that per investigator review has a reasonable possibility of being caused by the investigational product.

Overall Response:

Overall response definitions are given below for different indications.

Group 1 in dose-escalation cohort / Group 4 (R/R AML)

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*).

Group 2 (MRD+ AML)

Response is defined as conversion from MRD+ status with 0.1% threshold to MRD-.

Group 3 (MDS)

Response is defined as any of the following:

CR or marrow CR (all according to Revised IWG response criteria)

Group 5 and Group 1 in dose-expansion cohort (R/R AML)

Response is defined as any of the following: CRMRD-, CR, CRi, MLFS, PR.

Minimum Residual Disease (MRD) Response (All groups):

Minimum residual disease response is defined as MRD negative, indicating presence of leukemia cells to 0.1% or lower of white blood cells.

Overall Survival (OS)

Overall survival is defined as the time from enrollment until death due to any cause. Subjects alive will be censored at the last known date. 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 date of last contact through the analysis trigger date.

Event-free Survival:

Event-free survival (EFS) is defined as the interval from first administration of AMG 330 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 AMG330. For non-responders, the event date for treatment failure is assigned as the date of first administration of AMG 330.

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 330 +1.

Event-free Survival in months = earlier of (date of treatment failure or relapse or death or date of censoring) – (date of the first administration of AMG 330 +1)/30.4.

Time to Response (TTR):

Time to response defined as the interval from the first administration of AMG 330 to the first documentation of confirmed response. Time to remission 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).

Section: Analysis Sets, Planned Analyses
Replace:

Dose Limiting Toxicity Analysis Set:

The Dose Limiting Toxicity Analysis Set will contain DLT-evaluable subjects (see protocol section 3.4 for definition of DLT-evaluable). Responder Analysis Set. The response analysis set will contain all subjects with objective responses [complete remission (CR), CR with incomplete recovery (CRi) or CR with partial hematologic recovery (CRh*)].

Interim Analysis and Early Stopping Guidelines:

No formal interim analysis will be conducted. Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigator, will review in Dose Level Review Meetings (DLRMs) all available cumulative data by cohort prior to 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.
With:

Dose Limiting Toxicity Evaluable Analysis Set:

The DLT-evaluable Analysis Set includes all DLT-evaluable subjects. The analysis of DLT will be restricted to the DLT-evaluable Analysis Set. A subject is not DLT-evaluable if he/she drops out before completion of the DLT window for reasons other than an adverse event related to study drug or the subject has not received IP treatment for at least 14 days at the target dose for a 3- or 4-week cycle or at least 7 days at a target dose for a 2-week cycle. Furthermore, following drug interruptions, if a subject is unable to complete 2 repeat cycles for reasons other than DLT, the subject will not be DLT evaluable.

Interim Analysis and Early Stopping Guidelines:

Interim analyses are planned after all subjects in each indication and each phase have ended the study eg, for R/R AML: all subjects enrolled in Group 1 phase 1a, Groups 4 and

5 have ended the study. Interim analyses may be combined if the analysis timing is close or if the number of subjects in each indication or phase is small. Formal interim analyses will be based on locked database.

Ad-hoc interim analyses for safety and preliminary efficacy updates will be performed. Data analysis prior to public disclosures (e.g. scientific meetings) will also be performed. Safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigators, will review in DLRMs all available cumulative data prior to making dose escalation decisions. For R/R AML (Group 1), dose escalation decisions will be made in accordance with a standard 3+3 design using the rules noted below.

- If no DLT is observed within the DLT window in the initial 3 subjects of a cohort, then dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed within the DLT window in the initial 3 subjects of a cohort, then the cohort will be expanded to 6 subjects. If no further DLT(s) are observed in the 6 subjects, then dose escalation to the next higher dose level cohort will occur. If ≥ 2 subjects experience a DLT in a cohort, then enrollment into this cohort will be stopped.

Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose level with an observed incidence of DLT in < 33% of subjects enrolled in a cohort dose level. At least 6 evaluable subjects will be treated at the MTD or highest tested dose.

The mTPI-2 model will be used to make dosing recommendations for Group 2 and Group 3 (see section 3.3 for details). 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.

Enrollment of a cohort can be suspended at any time based on safety findings at any dose level and in the expansion cohort, if at any time ≥ 33% of subjects treated at the MTD (including those treated at the MTD in the expansion phase) or RP2D experience a DLT within the DLT window, and a DLRM will be convened. In addition, the study may be discontinued or modified at any time due to documented safety findings.

Added:

Analysis Sets:

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety analysis set defined in Section 6.1.

Planned Analyses:

The following data analyses are planned: (1) dose decision analyses in the dose-escalation cohorts, (2) interim analyses for safety and preliminary efficacy updates, (3) data analysis prior to public disclosures (e.g. scientific meetings), (4) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (5) the final analysis after all subjects have ended the study.

Dose Level Review Team (DLRT):

For each group, DLRMs will be held to review data, monitor safety, and make recommendations 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, global safety officer or designee, clinical study manager, biostatistician, PK scientist (optional), and other functional area representatives as appropriate. A quorum as defined below must be in attendance for the DLRM. The quorum is defined as > 50% of the participating investigators 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 required voting members of the DLRT include: investigators, Amgen medical monitor, early development leader, and global safety officer or designee.

The following recommendations can be made by the DLRT:

- dose escalation / de-escalation decisions
- expansion of a cohort
- continuation, delay or termination of dosing
- implementation of dose step(s)
- extension of the run-in phase in case of dose step(s)
- extension of the duration of treatment cycles
- implementation of mandatory steroid pre-treatment in case of cytokine release syndrome-related adverse events
- enrollment of additional subjects in the expansion cohort
- duration of the DLT period based on emergent safety data
- level and duration of dose steps (schedule) adjustment based on safety, and available PK and PD data

All available study data, 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 recommendations. Data will not need to be source data verified and queries will not need to be resolved prior to the DLRM. Subject's cytogenetic profiles (eg, potentially higher cytokine release in monocytic AML) should be taken into consideration for DLRT recommendations.

In the expansion phase, all available study data will be reviewed (with recruitment ongoing) by the DLRT once the first 5 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment / study, whichever occurs earlier. Once the first 10 subjects have at least completed their first treatment cycle plus two weeks or dropped out of study, all available study data will be reviewed by the DLRT. If there is at least 1 responding subject within these first 10 subjects, the DLRT will determine if an additional (up to 20) subjects may be enrolled. If additional subjects are enrolled after the first 10 subjects, all available study data will be reviewed (with recruitment ongoing) by the DLRT after every 5 subjects have at least completed their first treatment cycle plus two weeks or dropped out of treatment / study. Ad hoc meetings may be convened any time in case of important safety events.

Primary Analysis:

The primary analysis will occur when target enrollment is complete and each subject either completes 6 months on study or terminated the study early. Primary analysis will be based on locked database to prevent further changes

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 approximately 6 months after enrollment of the last study subject. Final analysis will be based on locked database to prevent further changes

Section: Data Screening and Acceptance

Replace:

Validation of Statistical Analyses:

for example the SAS System and S-plus.

With:

Validation of Statistical Analyses:

for example the SAS System version 9.4 or later.

Deleted:

Outliers:

Outlier data will not be excluded unless scientifically justified.

Added:

Data Handling and Electronic Transfer of Data:

This study will use the RAVE database.

Handling of Missing and Incomplete Data:

- 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.
- PD concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PD parameters.

Outliers:

Pharmacodynamic (PD) concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard PD evaluation practice. Descriptive statistics will be used to identify potential outliers in key variables.

Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

Section: Statistical Methods of Analysis

Replace:

Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later will be used to code all adverse events to a system organ class and a preferred term. The subject incidence of adverse events will be summarized for all treatment-emergent, serious treatment emergent, treatment-related, serious treatment-related, those leading to withdrawal of investigational product, fatal, and of special interest (if applicable). The identification of adverse events of special interest is a continuous process. Events may be identified and documented as the safety profile of the drug is characterized. The severity of each adverse event will be graded using CTCAE version 4.0 criteria.

Subject incidence of all treatment-emergent, serious, treatment-related, serious treatment-related, suspected immune-related, those leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency. Where appropriate the tables will also be presented by worst grade. Listings and/or narratives of any on-study deaths, serious and significant treatment-emergent adverse events, including early withdrawals due to adverse events, also will be provided should they occur.

Laboratory Test Results:

Clinical chemistry, hematology, and urinalysis data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time will be provided and tables of maximum shifts from baseline for selected laboratory values will be provided.

Vital Signs:

Vital signs 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 will be provided. Vital signs (resting systolic/diastolic blood pressure, heart rate, respirations, and temperature in a supine position for at least 5 minutes) will be summarized using descriptive statistics.

Summary statistics for each vital sign parameter will be provided for baseline and each scheduled post-baseline assessment, as well as the change from baseline at each of the post-baseline scheduled time points.

With:

Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

The subject incidence of adverse events (including disease related events) will be summarized for all treatment-emergent adverse events, 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 grade. In addition, SAEs and grade 3 and above adverse events will be summarized by preferred term in descending order of frequency.

The severity of each adverse event will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria with the exception of cytokine release syndrome (CRS), which will be graded using the criteria referenced in the publication by Lee et al (2014).

Subject incidence of events of interest (standardized MedDRA queries and/or Amgen customized queries) will also be summarized according to their categories and preferred term and worst grade. CRS will be summarized by grade and symptom.

TEAE summaries will be provided both by cohort and by overall groups.

Laboratory Test Result:

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

In interim, primary and final analyses, depending on the size and scope of changes in selected laboratory data, summaries of selected laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided. Unscheduled assessments will be included in these summaries.

Vital signs:

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

In interim, primary and final analyses, depending on the size and scope of changes, summaries of vital signs (resting systolic/diastolic blood pressure, heart rate, respirations and temperature) data over time and/or changes from baseline over time may be provided. Unscheduled assessments will be included in these summaries

Deleted:

Subject Accountability:

A subject listing and summary noting inclusion in each analysis subset will be provided for all subjects enrolled. A subject listing noting duration of AMG 330 administration, 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.

Important Protocol Deviations:

If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be updated during the IPD reviews throughout the study prior to database lock.

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.

Added:

General Consideration:

Additional analysis for Group 4 and Group 5 will be specified in SSAP.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper and Pearson (1934).

Important Protocol Deviations:

Eligibility deviations are defined in the protocol.

Demographic and Baseline Characteristics R/R AML:

ECOG performance status, Type of AML (at initial diagnosis and at study entry), Prior lines of therapies Responses to the prior lines of therapies, Prior hematopoietic stem cell transplant, Disease duration, Bone marrow blast, Baseline Tumor Burden, ELN risk classification, White blood cells, Absolute Neutrophil count, Platelet count.

Baseline characteristics for MRD:

Height, Weight, ECOG performance status, Type of AML (at initial diagnosis and at study entry), MRD Status, Prior lines of therapies Responses to the prior lines of therapies, Prior hematopoietic stem cell transplant, Disease duration, Bone marrow blast, Baseline Tumor Burden, ELN risk classification, White blood cells, Absolute Neutrophil count, Platelet count.

Baseline characteristics for MDS:

Height, Weight, ECOG performance status, Type of AML (at initial diagnosis and at study entry), Type of MDS (at initial diagnosis and at study entry), MDS Risk(IPSS-R) (at initial diagnosis and at study entry), MDS status at study entry, Prior lines of therapies, Responses to the prior lines of therapies, Prior hematopoietic stem cell transplant, Disease duration, Bone marrow blast, Baseline Tumor Burden, ELN risk classification, White blood cells, Absolute Neutrophil count, Platelet count.

Analyses of Primary Efficacy Endpoint(s):

No efficacy parameter is considered in primary endpoints.

Analyses of Secondary Efficacy Endpoint(s):

The proportion of subjects with an overall response (Section 5.4) with corresponding exact 80% and 95% Confidence Intervals will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) by cohort. The proportion of subjects who are event-free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method.

Listings indicating time to response, duration of response (DOR), and event-free survival will be produced for responders for each indication separately. For subjects in dose expansion cohorts, Kaplan Meier curves may be presented for event-free survival and overall survival with estimates for rates and 80□ CI at selected weeks. DOR and time to response will only be analyzed for subjects who achieved an overall response.

Analyses of Exploratory Efficacy Endpoint(s):

The following statistical analyses will be considered exploratory and will be performed by clinical biomarker group in Department of Translational Medicine only when deemed appropriate. Relationships between changes in tumor dynamics and above biomarkers of interest listed as exploratory endpoints will be explored. Changes in expression levels of biomarkers and their relationship to dose may also be explored. Summary statistics over time will be provided and graphical presentations may be used. The relationship between AMG 330 exposure and PD effects and related biomarkers in blood, or tumor specimens and/or AMG 330 exposure and clinical outcomes (eg, tumor response) will be also explored if deemed appropriate. Details of analysis will be provided in a Contributing Scientific Report for exploratory biomarker analysis. Pharmacodynamic (PD) biomarkers for AMG 330 mechanism of action (Depletion of LSCs, Lymphocyte counts, CD33+ monocytes ,T cells, T cell activation (including T cell subsets), Other immune subsets, [redacted].

Analyses of Primary Safety Endpoint:

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 330. Treatment groups will be defined based on the planned doses for Cycle 1.

Analyses of Dose Limiting Toxicities:

The analysis of Dose limiting toxicities (DLT) will be based on the DLT Evaluable Analysis Set. A listing and summary of the subject incidence of dose limiting toxicities (DLT) will be provided.

Physical Measurements:

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

Electrocardiogram (ECG):

In the event of extreme outlier readings, an additional sensitivity analysis will be conducted where the outlier measurement is excluded from the derivation of the mean for that assessment. The criteria used to define an outlier measurement will be determined based upon inspection of the data.

Antibody Formation:

All medication will be coded using the WHO drug dictionary. A subject listing of all concomitant medications will be presented for DLRM. In the interim, primary and final analyses, the number and proportion of subjects receiving concomitant medications will be summarized by preferred term for each treatment group and indication as coded by the World Health Organization Drug (WHO DRUG) dictionary.

Exposure to Concomitant Medication:

All medication will be coded using the WHO drug dictionary. A subject listing of all concomitant medications will be presented for DLRM. In the interim, primary and final analyses, the number and proportion of subjects receiving concomitant medications will be summarized by preferred term for each treatment group and indication as coded by the World Health Organization Drug (WHO DRUG) dictionary.

Section: Other Analysis

Added:

Analysis of PK or PK/PD Endpoints:

For AMG 330, pharmacokinetic parameters half-life, steady-state concentration, volume of distribution, and clearance) will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 330 exposure and either pharmacodynamic effect and/or clinical outcome may also be performed.

Serum concentrations of AMG 330 will be determined using a validated assay. Parameters to characterize cellular kinetics related to cell expansion (eg, C_{max}, T_{max} and partial AUC) and cell persistence (eg, $T_{1/2}$, T_{last} and C_{last}) in PBMCs, 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 cellular kinetic 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 Cellular kinetic analyses, including but not limited to analysis of the relationship between AMG 330 dose and exposure parameters (AUC and Cmax) and dose proportionality assessments, may also be conducted. Based on the review of the data, analyses to describe the relationship between AMG 330 exposure and either Pharmacodynamic effect and/or clinical outcome may also be performed.

A preliminary assessment of dose proportionality will be made using the Power Model Statistical analysis of $AUC_{(0-t)}$ and Cmax of AMG 330 will be performed after log transformation of the data. The Power Model:

$Y = \alpha\ dose^{\beta}$

where Y is the pharmacokinetic parameter and α is an intercept term. This becomes a linear relationship following a logarithmic transformation, to which a linear regression approach can be applied as,

$log(Y) = \beta \times log\ (dose) + log(\alpha)$

The coefficient of the slope with 90% confidence intervals, on the log scale, will be calculated.

Descriptive statistics will be provided for biomarker data by dose, dose schedule, and time as appropriate.

Analysis of Biomarker Endpoints:

Biomarker data may be incorporated in additional exploratory subgroup or multivariate analyses. The analyses of biomarkers will be considered exploratory and may be

performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis. Changes in expression or expansion level of biomarkers and their relationship to dose may be evaluated. Summary statistics over time may be provided and graphical presentations may be used. Details of analysis will be provided in Contributing Scientific Report for exploratory biomarker analysis.